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Hepatic vein obstruction is the most common type of hepatic venous outflow obstruction regardless of socioeconomic status

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Abstract

Background Data regarding role of socioeconomic status (SES) as etiology and site of involvement of veins in hepatic venous outflow tract obstruction (HVOTO) is scarce and only described from Nepal. We prospectively evaluated the role of SES in patients with HVOTO.

Methods 70 consecutive patients (41 females; mean age 29, range 3-65 years) with HVOTO were studied. Their clinical history, socioeconomic factors (income, education, and occupation), birth history, dietary factors, living standards, baseline characteristics, liver function, and clinical parameters were evaluated.

Results Of the 70 patients analyzed, 48 (68.5%) had hepatic vein (HV) obstruction, 7 (10%) had isolated inferior vena cava (IVC) obstruction, and 15 (21.5%) had combined HV and IVC obstruction. Of the 10 patients belonging to the upper SES, 7 had isolated HV obstruction, and 3 had combined IVC and HV obstruction; no patient had isolated IVC obstruction. Of the 60 patients belonging to the lower SES, 41(68.4%) had HV obstruction, and 19 (31.6%) had IVC involvement with (n=12) or without (n=7) HV involvement. HV/IVC involvement did not correlate with setting of delivery (hospital vs. home), birth weight, birth complications, immunization in childhood, ventilation in house, water storage facilities, history of diarrhea, or diet. Patients with HVOTO living in a mud house had IVC obstruction more commonly than HV (6/22 vs. 4/48; P=0.04).

Conclusion Isolated hepatic vein obstruction is the most common site of obstruction in patients with HVOTO in India, even among those belonging to low SES. Patients with HVOTO living in a mud house have IVC obstruction more commonly. Other socioeconomic factors studied do not appear to correlate with the site of obstruction.

Keywords Budd Chiari syndrome, socioeconomic status, inferior vena cavamembrane, hepatic venous outflowtract obstruction

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Introduction

Hepatic venous outflow tract obstruction (HVOTO) is defined as obstruction to hepatic venous outflow at any site from the right atrium inlet to the small hepatic venules [1]. The Budd-Chiari syndrome (BCS) results from occlusion of one or more hepatic veins (HV) and/or the inferior vena cava (IVC). In the West, the most common cause is HV occlusion by thrombosis. IVC obstruction, especially by an IVC membrane, has been traditionally believed to be common in India [2-5]. More recent Indian studies have however shown that isolated HV and combined IVC+HV obstruction are now more common [6,7].

Poverty, malnutrition, recurrent bacterial infection (all more common among the lower socioeconomic status, SES), tumors, pregnancy, oral contraceptive pill intake have been suggested as possible reasons for the earlier difference in pattern of anatomy of HVOTO between India and the West [8]. In Nepal, where IVC membrane is predominant, 89% patients with HVOTO are from the lower SES [8]. In the West, a prothrombotic state has been identified in up to 90% of patients with HVOTO [1] Most of these patients have HV thrombosis with or without IVC involvement. Prothrombotic states were reported to be relatively uncommon in HVOTO in earlier Indian studies [6,7]. Recently, two studies from India for prevalence of *JAK2 V617F* mutation in patients with HVOTO have shown variable results, 40% in one [9], and 8.8% in another [10].

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According to one hypothesis, poor hygiene and low SES may be associated with IVC membrane, and improved standards of living may result in lower incidence of IVC membrane [11]. No data exist regarding SES and its etiological role in patients with different types of HVOTO. We therefore compared patients with HV and IVC obstruction to determine if there is any role for socioeconomic factors in the predilection for site of obstruction. We also wanted to assess whether IVC obstruction is still the most common form of HVOTO among Indian patients with low SES.

Patients and methods

This was a single-center prospective cross-sectional observational study. Seventy consecutive patients with BCS, diagnosed by color Doppler and magnetic resonance (MR) venography, who presented to our liver clinic between November 2010 and April 2012, were evaluated. Written informed consent was taken for inclusion in the study. The study was approved by the institution's ethics committee.

Details of demographic characteristics, dietary factors, birth history (birth place, birth weight, birth complications, immunization in childhood), socioeconomic factors (income, education and occupation), history of diarrhea and living standards (type of house, ventilation in house, water storage facilities) were recorded, in addition to clinical history and features and liver function tests.Patients with significant alcohol history, chronic viral hepatitis or any other potential cause of chronic hepatitis or cirrhosis were excluded from the study. Modified Kuppuswamy's classification (Table 1) was used for definition of SES [12]: classes I and II were considered as upper SES; and classes III, IV and V were considered as low SES. Patients' current SES data were collected and analyzed. Anatomy of the HV and IVC along with the pattern of obstruction were noted. On MR venography (and IVC angiography when performed), IVC obstruction <1 cm in length was defined as IVC membrane.

Statistical analysis

The distribution of the SES and the type of HVOTO was analyzed. Univariate analysis was done using chi-square test to find the association between subtypes of BCS and various socioeconomic factors. Binomial logistic regression was used to find the predictivity of different factors in vein involvement. $P<0.05$ was taken as significant for all the statistical tests. Statistical analysis was done using SPSS software 16.0.

Results

Of the 70 patients (41 females; mean age 29, range 3-65 years) with BCS, 48 (68.5%) had HV obstruction, 7 (10%) had isolated IVC obstruction, and 15 (21.5%) had combined HV and IVC obstruction. Eighteen patients were ≤20 years of age, while 50 were aged 21-60 years, and two were above 60 years of age. Two patients belonged to class I, 8 to class II, 20 to class III, and 40 class IV. Of the 10 patients belonging to the upper SES, 7 had isolated HV obstruction, and 3 had combined IVC and HV obstruction; no patient had isolated IVC obstruction. Of the 60 patients belonging to the lower SES, 41(68.4%) had HV obstruction, and 19 (31.6%) had IVC involvement with (n=12) or without (n=7) HV involvement. There was no difference in anatomy of HVOTO among different age subgroups (Table 2).

Setting of delivery (hospital vs. home), birth complications, immunization status, and history of breastfeeding were not different between patients with isolated HV involvement and IVC involvement with or without HV involvement. Birth weight details were available in only 26 patients: of 17 patients with HV involvement 13 had low birth weight while 4 of 9 patients with IVC with or without HV involvement had low birth weight

Table 1 Kuppuswamy's socioeconomic status scale

Education score	
• Profession or Honors 7	
• Graduate or postgraduate 6	
• Intermediate or post high school diploma 5	
• High school certificate 4	
• Middle school certificate 3	
• Primary school certificate 2	
• Illiterate 1	
Occupation score	
• Profession 10	
• Semi-Profession 6	
• Clerical, Shop-owner, Farmer 5	
• Skilled worker 4	
• Semi-skilled worker 3	
• Unskilled worker 2	
• Unemployed 1	
Family income per month (in US dollars [as calculated from original scale of rupees])-modified in 2007	
• >319.70	12
• 159.86-319.69	10
• 119.60-159.85	6
• 79.93-119.59	4
• 47.95-79.92	3
• 16.01-47.94	2
• <16.01	1

Total score	Socioeconomic status
26-29	Upper (class I)
16-25	Upper Middle (class II)
11-15	Lower Middle (class III)
5-10	Upper Lower (class IV)
<5	Lower (class V)

(P=0.03). On analysis of diet type, the upper SES consumed more fruits and vegetables, while the lower SEC consumedmore rice, dal (pulses), groundnut oil and non-vegetarian food in their diet. This difference did not correlate with the site of obstruction (Table 3).

There was no difference in ventilation in house, number of rooms, toilet availability in house, separate bathroom, and type of water-storage facility in relation to site of venous obstruction. Of 48 patients with HV involvement 4 had mud houses, while of the 22 patients with IVC with or without HV involvement 6 had mud houses (P=0.04)(Table 4).

Twenty-one percent of patients had received anti tuberculosis drugs prior to the diagnosis of BCS. History of diarrhea prior to the onset of symptoms was present in only three (4.2%) cases.

Details of prothrombotic state were available in only some patients (Table 5). There was no history of major intra-abdominal infection, abdominal surgery, abdominal trauma or inflammatory bowel disease in any patient. Two patients had a history of oral contraceptive pill ingestion. No patient had deep vein thrombosis, cerebral stroke or varicose veins. None of the study group patients had liver malignancy or history of diagnosed/treated parasitic liver infection.

Table 2 Age, gender and socioeconomic status (SES) in relation to level of obstruction in patients with of hepatic venous outflow obstruction (n=70)

	No.	Obstruction level			P value*
		HV (n=48)	IVC (n=7)	HV+IVC (n=15)	
Age (years)					
0-20	18	12	3	3	0.903
21-40	25	17	1	7	
41-60	25	17	3	5	
61-80	2	2	0	0	
Sex					
Male	29	19	3	7	0.89
Female	41	29	4	8	
SES					
Upper	10	7	0	3	0.79
Lower	60	41	7	12	

HV, hepatic vein; IVC, inferior vena cava; *Univariate analysis

Table 3 Birth details in relation to level of obstruction in patients with hepatic venous outflow obstruction (n=70)

	No.	Obstruction level			P value*
		HV	IVC	HV+IVC	
Setting of delivery					
Hospital	30	18	3	9	0.31
Home	40	30	4	6	
Birth weight (Kg)					
Details not available	44	31	6	7	0.03
Low (<2.5)	17	13	1	3	
Normal (≥2.5)	9	4	0	5	
Birth complication					
None	49	33	5	11	0.941
Neonatal infection	20	14	2	4	
Jaundice	1	1	0	0	
Immunization					
Yes	56	38	6	12	0.92
No	14	10	1	3	

*Univariate analysis

Discussion

This study was done to evaluate social, economic, environmental and dietary factors in patients with BCS in

Table 4 Residence, diet and infectious illnesses in relation to level of obstruction in patients with hepatic venous outflow obstruction (n=70)

	No.	Obstruction level			P value*
		HV (n=48)	IVC (n=7)	HV+IVC (n=15)	
House					
Mud	10	4	3	3	0.04
Cement	60	44	4	12	
Ventilation in house					
Yes	52	38	4	10	0.34
No	18	10	3	5	
Storage of water					
Boiled	7	5	0	2	0.406
Unboiled	49	35	6	8	
Filter	14	8	1	5	
Diet					
Vegetarian	21	15	2	4	0.94
Mixed	49	33	5	11	
Fruit intake per week					
Daily	21	16	0	5	0.28
2-3 days	14	11	3	0	
Once	21	12	3	6	
Occasionally	13	8	1	4	
Never	1	1	0	0	
Main cereal content in food (>50% of intake)					
Wheat	50	31	5	14	0.06
Rice	20	17	2	1	
Cooking oil					
Groundnut	54	37	5	12	0.97
Sunflower	10	7	1	2	
Cottonseed	6	4	1	1	
Diarrhea (within previous 4 weeks of index event)					
Yes	3	1	1	1	0.29
No	67	47	6	14	
Received anti-tuberculosis treatment in past					
Yes	15	8	3	4	0.25
No	55	40	4	11	

HV, hepatic vein; IVC, inferior vena cava; *Univariate analysis

Table 5 Prothrombotic states in relation to level of obstruction in patients with hepatic venous outflow obstruction (n=70)

Prothrombotic states	Obstruction level				
	No. studied	HV	IVC	HV+IVC	Total
JAK 2 mutation	40	3/25	0/5	1/10	4
Factor V Leiden mutation	34	2/20	0/4	2/10	4 (all heterozygous)
Protein C deficiency	20	3/12	0/4	1/4	4
Protein S deficiency	20	3/12	0/4	1/4	4
Antithrombin III deficiency	20	0/12	0/4	0/4	0
Anti-phospholipid antibody	26	2/18	0/4	1/4	3
Paroxysmal nocturnal hemoglobinuria	22	0/14	0/4	0/4	0

HV, hepatic vein; IVC, inferior vena cava; JAK-2, Janus kinase 2

western India, and their association with the site of venous involvement.

Over two-thirds of our patients had HV obstruction alone; the rest had IVC involvement with or without HV obstruction. Earlier studies from India reported a high number of patients with IVC obstruction [2-5], but more recent studies showed HV as the predominant site of obstruction, as reported in Western countries [6,7,10,11]. A majority of our study population belonged to the lower SES, and over two-thirds of them also had isolated HV obstruction.

We assessed certain parameters of standard of living (birth place, birth weight, birth complications, immunization in childhood, type of house, ventilation in house, water storage facilities, history of diarrhea, diet) in addition to the components of the modified Kuppuswamy's classification [12]. Except for type of house (IVC obstruction was more common in patients living in mud houses), none of these parameters differed by site of venous obstruction.

Mud plastered houses are a known risk factor for visceral leishmaniasis but we are not aware of a similar risk factor in patients with BCS [13].

Shreshtha *et al* [8] reported that in Nepal, the majority of patients with BCS had IVC obstruction; 89% of their patients belonged to the low and the rest to the middle SES. Seventy-eight percent of their patients never went to school and only 3% had completed high school education; 61.3% were male. They hypothesized that diarrhea and post-partum pelvic infection could be major etiological factors leading to thrombosis in the IVC. In our study, done nearly two decades later, even among patients in the low SES, only one third had IVC obstruction (alone or in combination with HV obstruction). Only a few patients had a history of diarrhea preceding the index event and none had intra-abdominal infection.

One possible reason for this shift in site of obstruction even in the low SES over the years could be a general improvement in standard of living as compared to the poor of a few decades ago. For example, birth facilities, housing, sanitation, food type; prevalence of infectious disease may all be better now despite classification into the lower SES groups.

A limitation of our study is the small number of patients having isolated IVC obstruction. Prothrombotic conditions were not assessed in many patients due to financial constraints. Since ours is a government-funded hospital, a majority of patients belonged to the low SES and this is reflected in the number of patients belonging to the low SES in our study (60/70). There is no reason to believe that the findings will be different in high SES; recent Indian studies have confirmed such a shifting trend. The details of birth weight of patients with HVOTO were based on history provided by parents, and were available for only 26 patients; these data may be affected by recall bias and therefore no definite conclusions can be derived from them. Although there is no etiological correlation of use of anti tuberculosis therapy (ATT) in patients with BCS of different SES, many patients were inappropriately treated with ATT on the basis of high protein ascites prior to diagnosis at primary and secondary level centers. This indicates need for awareness for this disease (BCS) amongst primary and secondary healthcare providers.

In a previous study at our center, we had highlighted the challenges posed in treatment of financially challenged patients with HVOTO and showed that medical therapy alone is effective in a good proportion of patients [14].

In conclusion, our study shows that, in India, isolated hepatic vein obstruction is now the most common site of obstruction in patients with HVOTO, even among those

Summary Box

What is already known:

- Hepatic vein thrombosis is the most common type of hepatic venous outflow obstruction (HVOTO) in the West, while IVC membrane is more common in the East
- Diarrhea and low socioeconomic status (SES) have been implicated as a risk factor for inferior vena cava (IVC) membrane
- The incidence profile of HVOTO is changing in India with increasing incidence of hepatic vein thrombosis

What the new findings are:

- Hepatic vein thrombosis is the most common type of HVOTO in India even amongst patients of low SES
- The socioeconomic factors do not correlate with the type of HVOTO except for mud houses which was associated with IVC membrane

belonging to low SES. This reflects a change in spectrum over the years. The socioeconomic factors we studied do not appear to influence the site of obstruction.

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