

Hepatoportal Sclerosis in Childhood: Descriptive Analysis of 12 Patients

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Hepatoportal sclerosis (HPS) is defined as sclerosis of portal areas in the absence of cirrhosis. There is little information about HPS in children in the literature. The aim of this study was to describe the clinical presentation, associated disorders, laboratory characteristics and outcome of children who were diagnosed as HPS. This study included 12 children diagnosed as HPS by the Pathology Department between 2005 and 2011. Data were collected from the gastroenterology clinic charts retrospectively, including demographics, presentation characteristics, laboratory data and recent status of patients. Twelve patients were enrolled (6 girls, 6 boys). The median age of patients was 13.5 yr. Median age at the time of biopsy was 11 yr. Four patients had splenomegaly, 3 had esophageal varices, one had hepatopulmonary syndrome and had been transplanted. Smooth muscle antibody was found positive in 4 patients, without autoimmune hepatitis findings in liver biopsy. One patient had celiac disease and another patient had positive celiac disease serology but pathology findings. Another patient had Turner's syndrome. Mean follow-up time was 39 months (3.3 yr) after biopsy. Hepatoportal sclerosis does not necessarily present with portal hypertension in children.

Key Words: Hepatoportal Sclerosis; Idiopathic Noncirrhotic Portal Hypertension; Child

INTRODUCTION

Hepatoportal sclerosis (HPS) is a rare disease with unknown etiology. Historically, Banti (1) described this disease as morbus Banti in 1910. In 1965, Mikkelsen et al. (2) described 36 patients with splenomegaly and noncirrhotic portal hypertension and called this entity hepatoportal sclerosis. HPS is defined as sclerosis of portal areas in the absence of cirrhosis with patent portal and hepatic veins (2). There are various synonyms used to describe HPS like idiopathic portal hypertension, regenerative nodular hyperplasia, benign intrahepatic portal hypertension, non-cirrhotic intrahepatic portal hypertension, non-cirrhotic portal hypertension with portal fibrosis and incomplete septal cirrhosis (3). Mostly, case series were reported from India and Japan (4-6). There are also very well documented case series from the West (7). Finally, Schouten et al. (8) have published an extensive review and diagnostic criteria for idiopathic noncirrhotic portal hypertension (INCPH) in 2011.

In this study we aimed to describe the presenting symptoms, clinical and laboratory findings and interesting associations of patients with findings of HPS in their liver biopsies. Some associations we are describing here were not described before in patients with HPS. We also wanted to find out, if hepatoportal sclerosis as a pathological diagnosis represented a uniform clinical presentation and outcome in pediatric population. All, but

one, patients in this cohort had their liver biopsies done in our tertiary care institution due to various indications.

MATERIALS AND METHODS

This is a retrospective analysis of patients diagnosed with HPS between 2005 and 2011. Patients, who underwent liver biopsy due to various etiologies in our tertiary care centre and consequently reported as having findings consistent with hepatoportal sclerosis or portal venopathy by the Department of Pathology, were included. Seventeen patients' charts have been reviewed. One patient with Abernethy malformation in CT Angiography and additional 3 patients, who had either partial or complete portal vein thrombosis, were excluded from the study. One additional patient has been excluded from the study because of the missing data.

Patient demographics, clinical presentations, laboratory findings, imaging studies and outcome were noted from the clinic charts. Liver biopsies were done for all but one patient at the same institution with Menghini technique. All specimens were fixed in Bouin's solution and embedded in paraffin. Liver biopsy specimens then were stained with hematoxylin-eosin, Masson's trichrome and immunohistochemical CD34 stain, demonstrating periportal sinusoidal endothelialization. Pathology specimens were reviewed by single experienced pediatric pa-

thologist. All pathology specimens were examined to rule out cirrhosis, congenital hepatic fibrosis and hepatitis of viral, auto-immune and toxic origin.

Ethics statement

Ethics approval for this retrospective chart review analysis was exempted of review by institutional review board according to the law published in 2011 by the Turkish Ministry of Health. Consent from parents was not obtained due to same regulation. However, no additional blood tests or any analysis were done to collect data for this study.

RESULTS

Twelve patients were enrolled in this study (n = 12, 6 boys, 6 girls). Patient demographics and laboratory findings are shown

Table 1. Demographics of patients

Patient (No.)	Age (yr)	Sex	Age (yr) at biopsy	Follow up time after biopsy (months)	Associated findings	Outcome
1	12	M	10	52		CFU
2	16	F	15.1	39	Grade III varices	EVL
3	11.4	F	10.5	41	Turner syndrome	CFU
4	15	F	12	64		CFU
5	13.5	M	11.4	52		CFU
6	15.8	F	10.1	96		LTX
7	15.8	M	15.1	33	Grade III varices	EVL
8	1.5	M	2.3	38		CFU
9	11.2	F	11	27		CFU
10	1.5	M	0.9	29		CFU
11	17.9	M	17.6	21	Celiac disease	CFU
12	3	F	1.6	36	Grade II varices	CFU

CFU, Clinical follow-up without any complications; EVL, Endoscopic variceal ligation; LT, Liver transplantation.

Table 2. Laboratory findings of patients at presentation

Patient (No.)	ALT/AST	PT/INR	Albumin	WBC	PLT	Hb	SMA	Other
1	13/27	16.5/1.33	4.34	3,100	98,000	11.7	1/320 (+)	
2	106/164	15.9/1.42	2.90	3,900	59,000	11.4		
3	218/38	14/1.2	3.5	8,600	388,000	13.4		
4	170/100	13.5/1.02	4.35	6,800	332,000	13.6		
5	85/37	14/1	3.98	6,100	358,000	12.7		
6	13/24	17.8/1.5	4.10	4,000	98,000	13.5	(+), titer unknown	ACL IgG (+), ACL IgM (+)
7	99/87	14.2/1	3.03	11,300	329,000	14	(+), titer unknown	AGA* IgA (+) AGA IgG (+)
8	129/166	11.9/1	4.20	8,500	229,000	12		
9	67/94	11.7/1.03	2.48	12,800	137,000	11.1	1/20 (+)	
10	236/254	15.1/1.21	3.90	8,700	430,000	11.2		
11	45/35	14.1/1.10	4.30	2,790	110,000	6.3		AGA IgA (+) AGA IgG (+), tTG IgA (+), tTG IgG (+)
12	34/38	14.4/1.12	4.10	14,600	257,000	10.7		

ALT, Alanine aminotransferase (IU/L); AST, Aspartate aminotransferase (IU/L); PT, Prothrombin time (sec), INR, International normalized ratio; WBC, White blood cell in μ L; PLT, Platelet in μ L; Hb, Hemoglobin (g/dL); SMA, Smooth muscle antibody; ACL, Anti-cardiolipin antibody; AGA, Anti-gliadin antibody; tTG, Tissue transglutaminase antibody.

in Table 1 and 2. Median age at presentation was 10.7 yr (range 6 months-17.7 yr). Mean follow up time was 39 months (range 21-96 months). Two patients had weight percentile below the 3rd percentile (1 boy, 1 girl) at presentation. Five patients had incidentally discovered elevated liver enzymes at presentation. One patient had been referred from another tertiary care centre for liver transplantation after being followed for hepatopulmonary syndrome. Two patients had jaundice and elevated liver enzymes and one patient had pruritus at presentation. Another patient was referred from the Endocrinology Department when she was found to have elevated liver enzymes, where she was followed with the diagnosis of Turner syndrome. Nine patients had elevated ALT levels at onset. Median ALT for all patients was 92 IU/L (range 13-236 IU/L). Six patients had elevated AST levels. Median AST level for all patients was 62 IU/L (range 24-254 IU/L). Only one patient had elevated total bilirubin level (2.39 mg/dL). Mean bilirubin level was 0.82 mg/dL (range 0.14-2.39 mg/dL). Four patients had prolonged International Normalized Ratio with mean INR 1.16 (range 1-1.5). Five patients had thrombocytopenia (range 59,000-439,000/ μ L). Four of five patients had splenomegaly. All four patients also had low leukocyte count, which suggested hypersplenism. Mean leukocyte count was 7,600/ μ L (range 2,790-14,600/ μ L). Hemoglobin levels for age were low in all but 3 patients (median 11.85 g/dL, range 6.3-14 g/dL). One patient with significantly low albumin had been diagnosed with celiac disease. Three patients had low albumin levels (albumin < 3.5 g/dL). Mean albumin level for all patients was 3.75 g/dL (range 2.48-4.35 g/dL). Four patients had smooth muscle antibody (SMA) positivity. One of them had positive SMA in 1:320 titer, whereas the other was positive in 1:20 titer. Two patients had only qualitatively positive results. None of these patients had hypergammaglobulinemia and/or findings consistent with autoimmune liver disease in their liver biopsy specimens. One patient had positive anti-cardiolipin (ACL) IgG and IgM antibodies (40 and 46 phospholipid units respectively; < 22.9 units is negative). One patient had incidentally

tally diagnosed celiac disease, when an endoscopy was performed to check if he had varices. His anti-gliadin antibodies (AGA) and IgA and IgG anti-tissue glutaminase (tTG) levels have been found positive after the endoscopic biopsy. Another patient had positive AGA IgA and IgG positivity without celiac disease findings in duodenal endoscopic biopsy. Three patients had esophageal varices. Two patients, who had Grade III esophageal varices, underwent several band ligation treatments during their follow-up without any spontaneous variceal bleeding. The last patient with gastroesophageal varices had Grade II varices. All patients with gastroesophageal varices were on propranolol treatment. None of the patients had specific tests done for schistosomiasis and/or HIV, as they did not have clinical findings for either infection. Serology for hepatitis B and C infection including hepatitis B surface antigen, antibodies to hepatitis B core antigen and antibodies to hepatitis C virus were negative in all cases. None of the patients had drug or any substance exposure in their clinical history.

DISCUSSION

HPS is a rare condition in both pediatric and adult population. Mostly, pediatric data is extrapolated from adult cohorts (9, 10). Some of these cohorts contain small numbers of pediatric patients. On the other hand, there are some isolated pediatric case reports as well (11). Recently, Yilmaz et al. (12) have published a pediatric case series from Turkey, documenting cholestatic features in 12 Turkish children.

Hepatoportal sclerosis or INCPH can have serious and life threatening complications. One patient in our cohort had hepatopulmonary syndrome, improved after living donor liver transplantation. Kaymakoglu et al. (13) have reported hepatopulmonary syndrome in 2 patients with idiopathic portal hypertension. In their cohort there were 19 patients diagnosed with idiopathic portal hypertension and the prevalence was found 10.5%, which is similar to our results. However it is not mentioned in the article, whether these two patients have been transplanted or not. Isabel Fiel et al. (14) have reported a case series, consisting of 8 adult patients with HPS requiring liver transplantation. None of them was cirrhotic and 2 of them had portal vein thrombosis. Seven patients in this cohort had variceal bleeding as presenting symptom. When compared with our data, we had 3 patients with esophageal varices and none had variceal bleeding. Two patients in our cohort were treated with consecutive endoscopic variceal band ligation treatment without complications. All 3 patients with varices were on propranolol treatment. Krasinkas et al. (15) have reported 16 cases with noncirrhotic portal hypertension who underwent orthotopic liver transplantation. All were adult patients and none had hepatopulmonary syndrome. However, in this case series, 13 patients had clinical cirrhosis. Eleven of 13 patients had radiological evidence of cir-

rhosis and 4 had biopsy proven cirrhosis. Additional 3 cases who underwent liver transplantation have been reported by Geramizadeh et al. (16) in 2008.

Besides serious liver disease and associated complications, HPS has been reported in association with other diseases. Girard et al. (17) reported a child with Adams-Oliver syndrome and HPS. They have hypothesized that a vascular anomaly and thrombosis may be the etiology for this condition based on the fact that the patient had portal vein thrombosis and Factor V Leiden mutation. One year later, Pouessel et al. (18) have reported an additional child with Adams-Oliver syndrome. In our case series, none of the patients had Adams-Oliver syndrome, but we report an 11 yr old girl with Turner syndrome (TS). This patient had been referred by the Endocrinology Department in our institution, where she was found to have elevated liver enzymes incidentally, during a routine blood work. On physical examination, she did not have hepatosplenomegaly, or clinical findings consistent with portal hypertension, and remaining laboratory findings were normal. In the literature, liver disease in TS patients is reported to be common. Roulot et al. (19) have reported on vascular involvement of the liver in TS. They have included 27 TS patients with liver disease from 6 centers. They reported 10 patients with architectural changes in liver biopsy. Six patients had nodular regenerative hyperplasia (NRH), 2 had multiple focal nodular hyperplasia and 2 had cirrhosis. Among the patients with architectural changes, 4 had portal hypertension. Vascular lesions were shown in 2 patients with NRH, which was obliterative portal venopathy. Interestingly, they reported two patients with positive SMA, without hypergammaglobulinemia and autoimmune liver disease. In our cohort we had 4 patients with positive SMA. One of the problems with SMA autoantibody positivity in our cohort was that, 2 patients had only qualitative analysis and another had low titer positive results. None of the patients had hypergammaglobulinemia and/or autoimmune liver disease positivity in liver biopsy. However, in a study group of 12 children, positive SMA in 4 patients is probably not coincidental (33%). In a recent study from Brazil, seven hundred twenty-five healthy subjects were investigated for non-organ-specific autoantibodies. Approximately 10% of their cohort had positive SMA in 1:40 titer (20). In another study from Malaysia, 101 serum samples of 69 Malay, 18 Indian and 14 Chinese adults were studied for different autoantibodies including anti-nuclear, anti-mitochondrial, anti-smooth muscle and anti-parietal cell antibodies and none of 101 subjects had positive SMA (21). It is possible, different populations with different ethnic backgrounds have different autoantibody prevalence profiles in healthy populations. Unfortunately there is no published data available regarding the prevalence of SMA positivity in healthy Turkish population, which would help us making a comparison with our specific cohort. Although, it is not possible to make a conclusion with such small

Table 3. Comparison of idiopathic non-cirrhotic idiopathic portal hypertension (INCPH) diagnostic criteria published by Schouten et al. with findings in 12 patients

Diagnostic criteria of INCPH	Number of patients fulfilling criteria
Clinical signs of portal hypertension (any one of the following)	6
Splenomegaly/hypersplenism	4
Esophageal varices	3
Ascites (nonmalignant)	0
Increased hepatic venous pressure gradient	0
Portovenous collaterals	0
Cirrhosis on liver biopsy	0
Chronic liver disease causing cirrhosis or noncirrhotic portal hypertension such as chronic viral hepatitis B and/or C, nonalcoholic steatohepatitis/alcoholic steatohepatitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, primary biliary cirrhosis	0
Conditions causing noncirrhotic portal hypertension such as congenital liver fibrosis, sarcoidosis, schistosomiasis	0
Patent portal and hepatic veins (doppler ultrasound or computed tomography scanning)	12

numbers in our study, there might be an autoimmune process in etiology, affecting portal areas, causing ultimately sclerosis. In the presence of well described association of CD with HPS, the hypothesis of autoimmunity in the etiology of HPS becomes stronger, as CD is a known autoimmune condition.

Celiac disease (CD) and hepatoportal sclerosis has been reported previously in 2 adult cases. M'saddek (22) reported a 31 yr old patient with CD and splenomegaly. This patient did not have any abnormal liver function tests. Zamani et al. (23) have reported a 54-yr-old man with portal hypertension and CD, where his symptoms improved on a gluten-free diet. In pediatric age group, there are no published articles mentioning this association to the best of our knowledge. In our case series, one patient had been diagnosed incidentally with CD, where we were performing an upper GI endoscopy to check varices. His anti-gliadin antibodies and tissue transglutaminase antibodies found dramatically high afterwards. Another patient had positive anti-gliadin antibodies positive, without any CD findings in small bowel mucosa. These two children in our study group may be the first reported HPS patients; one with manifest CD, and the other with only positive serology, but the disease.

HPS has been described in some patients with HIV infection. Schiano et al. (24) have reported HPS in 2007 in 4 HIV (+) adults. They postulated that HPS might be due to intrahepatic microthrombosis or an altered hepatic fibrogenesis related to highly active antiretroviral therapy or due to HIV itself. Vispo et al. (25) have reported 12 HIV infected adult patients with HPS. All patients had been treated with a purine analogue, didanosine, for long time. Liver biopsies were available in 11 patients. None of the biopsies showed cirrhosis. Pathological diagnosis was HPS in 8 patients. They have postulated that, didanosine may have contributed to portal vein or its branches obliteration. In our cohort, none of the patients was tested for HIV infection. This was due to lack of risk factors, clinical and laboratory findings, which would raise the suspicion of HIV infection.

There are a lot of synonyms used for hepatoportal sclerosis. Schouten et al. (8) have used the term INCPH in their review in 2011. We have preferred to use hepatoportal sclerosis and not

INCPH just because our patients did not fulfill all the criteria required to make the diagnosis of INCPH (Table 3). There were children in our study group with hepatoportal sclerosis, who did not show symptoms of portal hypertension, but had associations described with INCPH and/or hepatoportal sclerosis. It was possible that, children did not develop portal hypertension findings at early stages and we have diagnosed these patients before portal hypertension findings have developed. We can speculate that children without portal hypertension might develop portal hypertension at some stage during their follow-up. Regarding the diagnostic criteria, some exceptions or modifications may be required for the diagnosis of INCPH especially in pediatric age group.

In summary, we wanted to investigate retrospectively, whether pediatric patients, underwent liver biopsy and been diagnosed with hepatoportal sclerosis, had a uniform presentation, including portal hypertension findings. We found out that, there was no uniformity among these patients. Patients in our cohort did not necessarily have findings of portal hypertension.

There are some weaknesses in this article. First of all, data had been collected retrospectively. There were some patients, where we could not collect all the data we aimed. Another weakness is, there might be some patients with HPS we are missing. Although they have HPS, these patients may not have been registered in the pathology database under the diagnosis of HPS, which may cause eventually issues with the power of the study. However, power is a chronic problem of pediatric cohorts in rare conditions, where it is extremely difficult to collect enough numbers of patients, unless multicentre studies or registries are planned ahead.

In conclusion, for pediatric age group with hepatoportal sclerosis findings in liver biopsy, who have not fulfilled the criteria for INCPH yet, it may be necessary to consider HPS as the initial diagnosis and once portal hypertension develops, INCPH diagnosis can be made. We need multi-center studies and registries to understand the characteristics of HPS in children in detail.

DISCLOSURE

Authors have no conflict of interest to disclose.

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