RISK FACTORS FOR VIRAL HEPATITIS B AND C INFECTION IN CHILDREN

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ABSTRACT

Objective: To determine the frequency of different predisposing illnesses and risk factors responsible for spread of chronic viral hepatitis in children.

Study Design: Descriptive study.

Place and Duration of Study: Department of Pediatric Gastroenterology, Hepatology, The Children's Hospital and the Institute of Child Health Lahore, from Jan to Dec 2016.

Material and Methods: Patients screened positive for HBV and HCV by HBsAg and Anti HCV were included in the study and further confirmation of infection was done by PCR and/or HBeAg. History regarding various risk factors and pre-existing illnesses was taken and all data was analyzed using SPSS version 20.

Results: Total 122 patients, mean age 9.86 ± 3.63 years, 89 male and 33 female; were included. Hepatitis B was found in 31 (25%) while hepatitis-C 91 (75%) patients. HCV genotype 3 was most frequent (69/91, 78%). Common pre-existing illnesses were: acute lymphoblastic leukemia 19 (15.57%), thalassemia 11 (9.02%), non-Hodgkin lymphoma 3 (2.46%), Hodgkin disease 2 (1.64%) and Celiac Disease 3 (2.46%). Hyperbilirubinemia (bilirubin >1.2mg/dL) was found in 15 (12.29%), elevated ALT (>42 iu/mL) in 49 (40.16) patients and ultrasound abnormalities in 21 (17%) patients. Most frequent risk factor was blood component transfusion present in 62 (51%) patients followed by perinatal transmission in 33(26%), history of viral hepatitis in father in 6 (6%) and history of surgery or dental procedure was present in 19 (16%) patients.

Conclusion: Hematological malignancies and thalassemia are the commonest predisposing conditions of HBC and HCV infection in children. Most common mode of transmission was blood transfusion present in nearly half the patients followed by perinatal transmission.

Keywords: Hepatitis B virus, Hepatitis C virus, Infection, Risk factors, Pediatrics.

INTRODUCTION

Chronic infection with hepato-tropic viruses (hepatitis B and C) is emerging as a cause of significant morbidity and mortality. In 2006, 93 million people were carriers of hepatitis B virus, with a prevalence of 7.18%. The carrier rate has decreased to a level of 6.1% by current year, mainly by routine vaccination against hepatitis B[1]. There is an estimate of 2.7 million people suffering from chronic hepatitis C infection in USA[2]. Estimated prevalence in Bangladesh is 0.6% with genotype C accounting for more than half the cases[3].

Data about prevalence of chronic hepatitis in Pakistani children is lacking. Prevalence of hepatitis B has been found to be 2.04% in Pakistani children in a small scale study conducted in Lahore in 1998 over 392 children[4]. Another study shows a 0.58% prevalence of HCV in children[5]. In Pakistani children with chronic liver disease, 31.66% were attributed to HCV and 5% to HBV[6].

In case of HBV, vertical transmission rate is 1.1% with administration of HBV immuno-globulins and vaccine at birth to the baby[7]. In patients on chronic blood component transfusion, frequencies as high as 9.2% for HBV and 54.2% for HCV have been reported from tertiary care setup in Pakistan[8]. Intranvenous drug abuse and hemodialysis have also been recognized as modes of transmission[9,10]. In a Pakistani study, risk factors for chronic HBV and HCV infection were surgery (32.55%), exposure to hepatitis

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patient (25.99%), foreign travel (20.25%) and blood transfusions (14.51%)[11].

In view of long term morbidity and complications of chronic viral hepatitis, including cirrhosis, hepatocellular carcinoma and need for liver transplantation, it is of utmost importance to implement preventive strategies and limit the spread of infection. Vaccination is the most convenient primary preventive measure for HBV. Vertical HBV transmission is also amenable to arrest by both active and passive immunization at birth. Contrary to HBV, no effective vaccine is available for HCV. It becomes pivotal to curtail the transmission by minimizing skin pricks, exposure to blood and blood products.

This study was planned to determine the frequency of predisposing illnesses and different etiologic factors responsible for spread of chronic viral hepatitis in Children presenting to the Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children's Hospital and the Institute of Child Health, Lahore.

MATERIAL AND METHODS

This descriptive study was done at the Department of Paediatric Gastroenterology, Hepatology and Nutrition, The Children's Hospital and the Institute of Child Health Lahore over a period of 12 months, from Jan to Dec 2016.

Sample size was calculated with confidence Level (1-α) 95%, absolute precision (d) 7% and expected frequency of transfusion associated transmission (P) 14.51%[11]. Sample size (n) was 122 cases. After approval from hospital ethical committee; Informed consent was taken from all patients' parents/guardian. Patients of either sex, aged under 18 years screened positive for HBV (HBsAg) and/or HCV (Anti HCV) were enrolled from both inpatient and outpatient along with patients referred from other departments of the hospital as well as other hospitals. Screening for both HBV and HCV was done in all patients. Further confirmation was done using real time PCR for HCV RNA and HBeAg or real time PCR for HBV. Patients having confirmed infection were included in the study by consecutive non-probability sampling. Screening positive patients who were negative on PCR or HBVeAg and patients who did not give consent were excluded from the study. Data was collected on especially designed proforma including the demographic information of each patient, including age, sex, any pre-existing condition (thalassemia, hemophilia, ALL, CKD etc.), history of blood component transfusions, history of injections, surgery, history of chronic viral hepatitis in parents.

Investigations including liver function tests and blood complete count were done from the hospital laboratory. Ultrasound abdomen of all patients was performed in the hospital's radiology department. Real time PCR for HCV RNA and HBV DNA was done in HCV and HBV positive patients respectively.

The collected data was analyzed statistically using SPSS version 20. Continuous variables like age, bilirubin, ALT, were subjected to normality testing using Shapiro-Wilk test. Variables having normal distribution were presented as mean and standard deviation while those having abnormal distribution were presented as median and interquartile range. Categorical variables such as gender, pre-existing conditions and various risk factors were presented in the form of frequency and percentage. Comparison between HBV and HCV groups was done. Independent sample t-test was used to compare means of quantitative variables having normal distribution, while Mann-Whitney U-test was used to compare non-parametric quantitative variables. Qualitative variables were compared using chi square/Fisher's Exact test. A *p*-value of less than 0.05 was considered significant.

RESULTS

Total 122 patients with hepatitis B or C virus infection were included in the study, 89 (73%) were male and 33 (27%) were female. Age range was between 3 to 18 years with a mean age of 9 ± 3 years. Hepatitis B was found in 31 (25%) patients while 91 (75%) had hepatitis C infection.

None of the patients had co-infection with both HBV and HCV. of all patients with hepatitis C, genotype 3 was found most frequent, constituting 69 (76%) out of 91 patients while genotype 1 was found in 8 (9%) patients. Genotype 2 was the most infrequent and found in only 2 (2%) patients while in 10 (11%) patients, genotype was untypable.

Hyperbilirubinemia (bilirubin >1.2mg/dL) was found in 15 (12.29%) patients out of which 3 (2.46%) had Criggler Najjar syndrome, 1 (0.82%) had concomitant acute viral hepatitis. A infection at the time of presentation and 1 (0.82%) had Wilson disease. Median bilirubin was 0.69mg/dL with an interquartile range of 0.38mg/dL. Elevated ALT (>42 iu/mL) was present in 49 (40.16%) patients while significant elevation of ALT (>100iu/mL) was seen in 26 (21.31%) patients. Median ALT was 39iu/ml with an interquartile range of 82.25iu/ml (table-I).

Table-I: Comparison of demographic data and liver fuctions (IQR = Interquartile Range).

	HBV (n=31)		HCV (n=91)		Significance	
Gender	Male	Female	Male	Female	*p*-value	
	26 (83.87%)	5 (16.13%)	63 (69.23%)	28 (31.77%)	0.11*	Insignificant
Age (Years)	Mean	SD	Mean	SD		
	9.49	4.04	10.03	3.44	0.57**	Insignificant
	Median	IQR	Median	IQR		
Bilirubin (mg/dL)	0.70	0.30	0.60	0.50	0.55***	Insignificant
ALT (iu/mL)	33	175	49	80	0.97***	Insignificant

*Chi square, **Independent sample t-test, ***Mann Whittney-U

Out of all 122; 55 (45%) patients had pre-existing illnesses; 19 (15.57%) had acute lymphoblastic leukemia, 11 (9.02%) had thalassemia, 3 (2.46%) had non-Hodgkin lymphoma, 2 (1.64%) had Hodgkin disease, 3 (2.46%) had Celiac disease, 3 (2.46%) had Criggler Najjar syndrome type 2, 2 (1.64%) had lymphoblastic lymphoma, 1 (0.82%) each had hemophilia, hypofibriniginemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, Fanconi anemia, atypical nephrotic syndrome, chronic kidney disease, congenital hepatic fibrosis, cerebral palsy, Wilson disease, tuberculous meningitis and Down syndrome each. All the three patients with Criggler Najjar syndrome were siblings and had perinatal transmission of HBV from mother which makes it a spurious association. All the three patients with celiac disease had history of blood component transfusion of the 31 patients with HBV infection, 22 (70.97%) had received 3 doses of HBV vaccine while 9 (29.03%) were unvaccinated against HBV. None of the patients with perinatally transmitted HBV infection received HBV immuneglobulin prophylaxis at birth.

Ultrasound abnormalities were present in 21 (17.21%) patients. In patients without any pre-existing illness, 6 (4.92%) had abnormal findings on ultrasound abdomen, 3 (2.46%) in the shape of hepatomegaly and 3 (2.46%) with altered liver texture. In patients with pre-existing illnesses, 15 (12.29%) had abnormalities on ultrasound abdomen; hepatomegaly was present in 4 (3.28%) patients; 2 (1.64%) with non-Hodgkin lymphoma and 2 (1.64%) with acute lymphoblastic leukemia, while hepato-splenomegaly was seen in 10 (8.20%) patients, 7 (5.74%) with thalassemia and 3 (2.46%) with acute lymphoblastic leukemia. Hepato-splenomegaly with altered liver texture and mild ascites was seen in 1 (0.82%) patient who was a case of CLD secondary to Wilson Disease (table-II).

Regarding risk factors elicited, most frequent risk factor was blood component transfusion. Ablut 62 (50.82%) patients had received transfusion of one or more blood components. Out of those, 29 (23.77%) had history of packed

red cell transfusion, fresh frozen plasma transfusion in 4 (3.28%), platelet concentrates transfusion in 1 (0.82%) while 28 (22.95%) had history of transfusion with more than 1 or all 3 blood products. Perinatal transmission from mother was documented in 33 (27.05%) patients

Table-II: Pre-existing illnesses.

	HBV (n=31) Freq. (% age)	HCV (n=91) Freq. (% age)	*p*-value	
Hematologic Malignancy	9 (29.03%)	15 (16.48%)	0.13*	Insignificant
ALL	7 (22.58%)	12 (13.87%)	0.21*	Insignificant
Hodgkin Lymphoma	1 (3.22%)	1 (1.10%)	0.44**	Insignificant
Non-Hodgkin Lymphoma	1 (3.22%)	2 (2.20%)	1.00**	Insignificant
Thalassemia Major	1 (3.22%)	10 (10.99%)	0.29**	Insignificant
Criggler Najjar Syndrome	3 (9.68%)	0 (0%)	0.01**	Significant
Celiac Disease	0 (0%)	3 (3.30%)	0.57**	Insignificant
Fanconi Anemia	0 (0%)	1 (1.10%)	1.0**	Insignificant
Hemolytic Anemia	0 (0%)	1 (1.10%)	1.0**	Insignificant
Hypofibrinogenemia	0 (0%)	1 (1.10%)	1.0**	Insignificant
Idiopathic Thrombocytopenic Purpura	0 (0%)	1 (1.10%)	1.0**	Insignificant
Atypical Nephrotic	1 (3.22%)	0 (0%)	0.25**	Insignificant
Congenital Hepatic Fibrosis	0 (0%)	1 (1.10%)	1.0**	Insignificant
Chronic Kidney Disease	0 (0%)	1 (1.10%)	1.0**	Insignificant
Cerebral Palsy	0 (0%)	1 (1.10%)	1.0**	Insignificant
Down Syndrome	0 (0%)	1 (1.10%)	1.0**	Insignificant
Wilson Disease	0 (0%)	1 (1.10%)	1.0**	Insignificant

*Chi square, **Fisher's Exact

Table-III: Risk Factors for HBV and HCV Infection.

	HBV (n=31) Freq. (% age)	HCV (n=91) Freq. (% age)	*p*-value*	
Blood Transfusions	10 (32.26%)	51 (56.04%)	0.08*	Insignificant
Perinatal Transmission	13 (41.93%)	20 (21.98%)	0.03*	Significant
Surgery	1 (3.22%)	13 (14.28%)	0.18**	Insignificant
Horizontal Transmission (Father)	3 (9.68%)	3 (3.30%)	0.13**	Insignificant

*Chi square, **Fisher's Exact

while 6 (4.92%) patients had history of viral hepatitis positive in father. History of surgery or dental procedure was present in 19 (15.57) patients while 3 (2.46%) had history of stitches application after minor wounds (table-III).

DISCUSSION

Hepatitis B and C infection is very common in adult population and a rapidly emerging problem in Pediatric population. This is mainly attributed to inadequate blood donor screening which is done by kit method in most of the blood banks of the country[9]. However, transmission by blood products has largely been eliminated in the developed countries by effective screening using ELISA of PCR based methods[12].

Mean age at presentation in present study was 9.68 ± 3.63 years and male to female ratio was roughly 3:1. Mean age of children with hepatitis B was 9.49 ± 4.04 and male to female ratio was roughly 5:1 while the mean age of children with hepatitis C infection was 10.03 ± 3.44 and a male to female ratio of 2:1. These

results conform to the results of existing local literature. In a study by Khan A on Pediatric hepatitis B infection, mean age was 8.4 ± 4.5 years which positively correlates with results of the present study. Male to female ratio; however, in the study of Khan et al was approximately 1.5:1 which is significantly lower than the results of present study[12]. Higher frequency of male patients could be because of social factors resulting in preferential presentation to hospital[14]. In a study done by Aziz et al on HCV infection in children and adolescents, mean age was 18.42 ± 2.59 years and a male to female ratio of 1:2.6 both of which are in contradiction to the present study[15]. However, the male to female ratio in HCV infection, in study done by El-Shabrawi et al is 1.7:1 which is somewhat concordant with the results of present study[16].

Hematological malignancies and thalassemia have been associated historically with a high frequency of viral hepatitis; especially HCV. In a study by Fujii et al in Japan 70% of leukemia patients were positive for anti-HCV[17]. Frequency of Hepatitis C in chronically transfused thalassemia patients in London was also as high as 23.3% couple of decades ago[18]. The rate of HCV was as high 91.8% in patients receiving multiple transfusions in a French study done over two decades ago; While, HBV was found at a much lower rate[19].

This situation is largely similar to the current situation in the developing countries. In a study done in Oman by Al-Naamani et al, 41% of patients with thalassemia were found to be anti-HCV positive[20]. However, in a recent small scale study done in Iran, all transfusion dependent thalassemia patients were found to be negative for HCV and HBV; suggestive possibly of an effective donor screening program[21]. Blood transfusion associated transmission to has decreased to negligible levels in the west[22] with most of the cases attributable to vertically transmitted infection[23].

In present study, Thalassemia was found much more frequently in patients with HCV than HBV hematological malignancies were much more frequenty found in association with HBV infection than HCV. No such clear one to one comparison could be found in literature; however, a study by Williams et al[24] has found a higher frequency of HCV infection in patients with thalassemia than HBV which is in concordance with the results of present study. Another study by Ocak et al[25] has produced similar results showing a higher frequency of HCV in patients with Thalassemia than HBV.

As eluded in the previous section; the association between Crigler Najjar Syndrome and HBV infection was a spurious one as all the three patients were sibling and had perinatal transmission from mother. Celiac Disease was a pre-existing ailment found in 3 patients with HCV infection but none in HBV infection. The difference between the two groups was statistically insignificant. All the three patients had history of packed red blood cells transfusion. Some studies have suggested that Celiac Disease might be associated with an inadequate response to Hepatitis B vaccination resulting in increased vulnerability towards HBV infection[26].

Perinatal transmission was the second most common mode of transmission in present study, in both HCV and HBV. No measures are available to prevent perinatal transmission of HCV. Procedures like amniocentesis and invasive intra-partum fetal monitoring increase the risk of transmission and should be avoided[27].

Use of anti viral agents to keep maternal HBV DNA load to minimum possible level and immune-prophylaxis with HBV Immune globulin and recombinant HBV vaccine administered at birth at different sites to the newborn can potentially prevent perinatal transmission of HBV infection[28].

Surgical procedures were identified as risk factors in 14 (14.43%) patients. Studies done elsewhere have also documented an increased risk for transmission of viral hepatitis in association with different surgical and dental procedures[29,30].

CONCLUSION

HCV was encountered thrice more frequently than HBV in Children. Common associated pre-existing ailments in patients with HBV and HCV infection were hematological malignancies and thalassemia. Blood borne transmission was the commonest mode of transmission followed by perinatal transmission.

RECOMMENDATIONS

ELISA based screening of donated blood should be implemented. Screening of all pregnant females should be ensured.Yearly screening of children on blood transfusion therapy should be implemented. Anti-viral agents should be made widely available to facilitate treatment of HBV and HCV patients and also for HBV positive mothers in order to reduce viral load and prevent transmission to the baby. Birth dose and a 05 years booster of recombinant HBV vaccine should be added to EPI schedule. Anti HBV immune globulins should be made available at all obstetric units for immune prophylaxis of babies born to HBV positive mothers. A National committee of experts should be constituted to provide screening and treatment guidelines based upon indigenous data.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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