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Original article

Demographics of incidentally diagnosed chronic hepatitis B in teenagers in Bangladesh

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Abstract:.
Hepatitis B (HBV) is endemic in Bangladesh. A prevalence of 2.4-9.7 % in adult population has been documented in various studies. The magnitude of HBV infection among Bangladeshi children and adolescents is less known. Chronic hepatitis B (CHB) in teenagers commonly present with Immune tolerant phase. Subsets of these patients present in Immune clearance, Inactive carrier or Reactivation phase. However both Immune tolerant and Reactivation phase need evaluation in decision making during treatment. Teenagers between 13-19 year presenting with incidental diagnosis of HBsAg positivity with either HBeAg positive or negative chronic hepatitis B, with normal or minimally raised aminotransferase level with low or high HBV DNA were included in this study. This was a prospective randomized study. CHB patients were divided into two groups, Group A which was HBeAg positive (Immune tolerant) and Group B was HBeAg negative (Reactivation phase). All 21 patients were asymptomatic. 11 patients with HBeAg positivity (M:F = 10:1), 10 patients with HBeAg negativity (M:F = 7:1). ALT range in HBeAg positive population was 15-77 U/L (Mean 45.8 U/L), in HBeAg negative population was 16-46 U/L (Mean 30.6 U/L). HBV DNA level in HBeAg positive patients was 10^5 -10^{12}, mean 10^{10}, in HBeAg negative patients was 10^3 -10^7, mean 10^6, However HBV DNA was mostly low in HBeAg negative variety. Necro-inflammation 7 and above was present in 8 patients (72.72 %) in group A, 7 patients (70 %) in group B. Stage 3 fibrosis (F3)was present in 1 patient (9 %) in group A, 1 patient (10 %) in group B presenting with similar histologic activity index and fibrosis scores in both groups. Teenagers with chronic Hepatitis B are potential treatment candidates. So demographic studies with histologic scoring is needed as a guide to start treatment. Present study reveals presence of Group B (HBeAg negative) variant in teenagers. As compared to adult population Group B in teenagers presents with relatively benign disease in those having normal or minimally raised alanine aminotransferase levels.

Keywords:
Teenagers
Chronic hepatitis B (CHB)
hepatitis B virus (HBV)
Serum ALT
Serum bilirubin

1. Introduction

Chronic hepatitis B (CHB) is a silent endemic in Bangladesh. Bangladesh belongs to intermediate prevalence region of hepatitis B virus (HBV) infection with predominant genotypes D and C [1]. The magnitude of HBV

infection among Bangladeshi children and adolescents is less known. A few studies are carried out in school students reveal a prevalence of 2.3-3 % [2,3]. In adults, reports documents an intermediate level of endemicity with carrier rates varying from 2.4 to 9.7 percent of the population [4,5]. Acquisition of HBV during childhood is thought to be responsible for a large proportion of chronic hepatitis B infections in Bangladesh. The natural history of perinatally transmitted hepatitis B is four stages – Immune tolerance, Immune clearance, Immune control and Immune escape. Most children with chronic HBV infection are immune tolerant, with high viral replication, positive hepatitis B envelope antigen (HBeAg), high HBV deoxyribo-nucleic acid (HBV DNA) levels, and normal levels of alanine aminotransferases (ALT). This pattern is mainly seen in children infected at birth. The immune-tolerant phase may last long into adulthood. However, some of the infected children go into the Immune clearance phase. This phase is marked by active inflammation and elevated aminotransferases and may develop into fibrosis over time. Most individuals with a sudden elevation of aminotransferases undergo spontaneous HBeAg/anti-HBe seroconversion. After HBeAg clearance, aminotransferase levels gradually return to normal limits, with anti-HBe developing spontaneously. The majority of individuals who demonstrate this clearance enter an ‘‘Immune control/ Inactive carrier’’ state with normalization of aminotransferases, a reduction in HBV DNA levels, and improvement in hepatic inflammation. A fraction of patients enter Immune escape/Reactivation state marked by HBeAg negativity, anti HBe positivity, raised aminotransferase levels, raised HBV DNA levels. Commonly this phase is seen in adults, however we do find patients with HBeAg negative hepatitis B in teenage group probably due to early acquisition of hepatitis B. Transmission of this infection occurs in three stages of life (a) Perinatal from infected mother to babies, (b) Horizontal from person to person, (c) Sexual and blood borne in adults. The risk of becoming chronic carrier is much greater in children than in adults. Child infected perinatallly has 70-90 % chance of becoming carriers, those infected in first four year of life has 30 % chance, those

infected later has less than 10 % chance of becoming carriers [6]. The risk of development of hepatocellular carcinoma is particularly high in HBV perinatally infected patients [7].

2. Materials and methods

Teenagers between 13-19 year presenting with incidental diagnosis of HBsAg positivity with either HBeAg positive or negative were included in this study. Two groups of CHB patients were included, Group A which was HBeAg positive (Immune tolerant) and Group B was HBeAg negative (Immune escape/ Reactivation phase). This was a prospective randomized study. Written informed consent was obtained from each patient or their legal guardian before inclusion of patients into study. The study was conducted during the period of January 2008-December 2011 at a private clinic in Dhaka, Bangladesh. Inclusion criteria included HBeAg positive or negative teenage patients with normal (≤42 U/L) or minimally raised alanine aminotransferase (<2×ULN). Exclusion criteria included immune clearance or Immune escape phase with raised alanine aminotransferase (≥2×ULN) with raised HBV DNA (≥10^{4-5} copies/ml) where liver biopsy is not needed to start treatment or those patients unwilling to participate in the study. All cases were subjected to detailed history and thorough physical examination. In all of participants, serum ALT, serum bilirubin level and platelet count were measured using an auto analyzer and prothrombin time by Quick's method. The cut-off value for abnormal ALT was set at 42 U/L. HBsAg, HBeAg was checked by enzyme-linked immunos-orbent assay (ELISA) (Abbott Labs, Chicago). HBV DNA quantification was done by Real Time PCR based TaqMan chemistry (HBV Real-TM Quant Sacaca Biotechnologies srt, Italy). The lower limit of detection was 300 copies/ml. All patients underwent percutaneous liver biopsies done using a Tru-Cut biopsy needle under local anesthesia. Liver biopsies were done if the baseline prothrombin time was not prolonged more than three sec than the control value and the platelet count was more than 100,000/mm^3. The patients were followed at 15-min intervals for one hour

and then at 30-min intervals for another two hours. Patients were discharged 24 hours post-liver biopsy. Biopsies were scored using histologic activity index (HAI) score by a single histopathologist who was blind to the clinical and laboratory data of the patients. The data were analyzed using SPSS software.

3. Results

All 21 patients were asymptomatic, having history of incidentally detected HBsAg positivity. All were treatment naïve with no past history of receiving any anti-viral medications. Group A included 11 HBeAg positive patients with M:F = 10:1, Group B included 10 HBeAg negative patients with M:F = 7:3. ALT range was 15-77 U/L (Mean 45.8 U/L) in group A population, while it was 16-46 U/L (Mean 30.6 U/L) for Group B population. HBV DNA level in HBeAg positive patients was 10^5 -10^{12}, mean 10^{10}, in HBeAg negative patients was 10^3 -10^7, mean $10^{6,}$ However HBV DNA was mostly low in HBeAg negative variety. Necro-inflammation 7 and above was present in 8 patients (72.72 %) in group A, 7 patients (70 %) in group B. Stage 3 fibrosis (F3) was present in 1 patient (9 %) in group A, 1 patient (10 %) in group B. Mean histologic activity index in group A and B was 6.63 & 6.2 and fibrosis scores was 1 & 1.2 respectively; tab_s. (1, 2) & fig_s (1-6).

Table (1) Baseline parameters of patients

Variable	Groups	
	A (Immune tolerant)	B (Immune escape)
Number	11	10
M: F	10:1	7:3
Age range (years)	15-18	14-18
Mean yr	17.36	17.1
ALT range (U/L)	15-77	16-46
Mean (U/L)	45.81	30.6
HBV DNA range (copies/ml)	10^5 -10^{12}	10^3 -10^7
Mean	10^{10}	10^6
HAI range	2-12	3-9
Mean	6.63	6.2
HAI-F range	0-3	1-3
Mean	1	1.2

Table (2) Patient demographic characteristics and viral features

Patient No	Age	Sex	ALT (U/L)	HBeAg	Anti-HBe	HBVDNA copies/ml	USG	HAI	HAI_F
1	18	M	15	POS	NEG	10^5	Normal	2	0
2	18	M	55	POS	NEG	10^{12}	Normal	7	1
3	16	M	36	NEG	POS	10^4	Normal	7	1
4	18	M	28	NEG	POS	10^5	Normal	7	1
5	18	M	31	NEG	POS	10^4	Normal	9	3
6	16	F	46	NEG	POS	10^4	Normal	5	1
7	18	M	66	POS	NEG	10^7	CLD	12	3
8	18	M	35	POS	NEG	10^8	CLD	5	1
9	17	M	52	POS	NEG	10^{11}	Normal	7	1
10	17	F	45	POS	NEG	10^6	Normal	7	1
11	18	M	30	NEG	POS	10^4	Normal	3	1
12	17	F	16	NEG	POS	10^3	Normal	7	1
13	18	M	28	POS	NEG	10^{12}	Normal	7	1
14	14	M	24	NEG	POS	10^3	Normal	7	1
15	17	M	31	POS	NEG	10^{11}	Normal	7	1
16	18	M	44	POS	NEG	10^{12}	Normal	3	0
17	18	M	23	NEG	POS	10^7	Normal	7	1
18	17	M	56	POS	NEG	10^6	Normal	7	1
19	15	M	77	POS	NEG	10^9	Normal	9	1
20	18	M	38	NEG	POS	10^4	Normal	3	1
21	18	F	34	NEG	POS	10^7	Normal	7	1

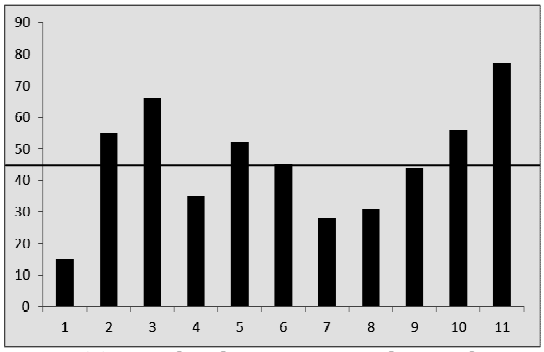

Figure (1) ALT levels in Immune tolerant phase

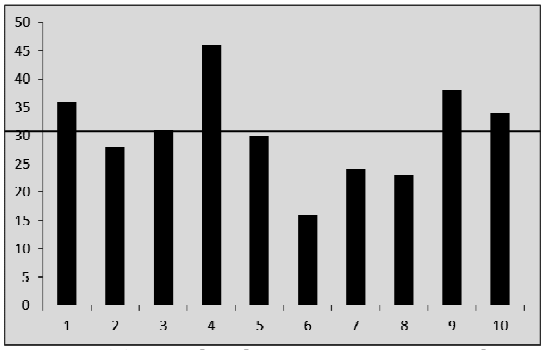

Figure (2) ALT levels in immune escape phase

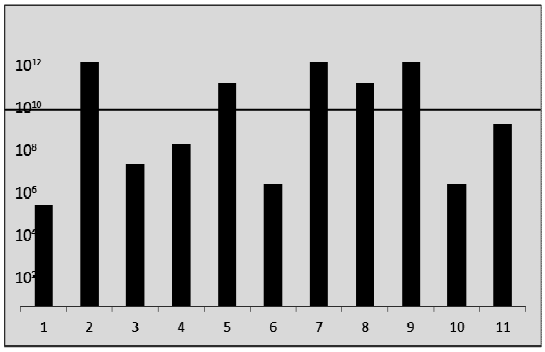

Figure (3) HBV DNA levels in Immune tolerant phase

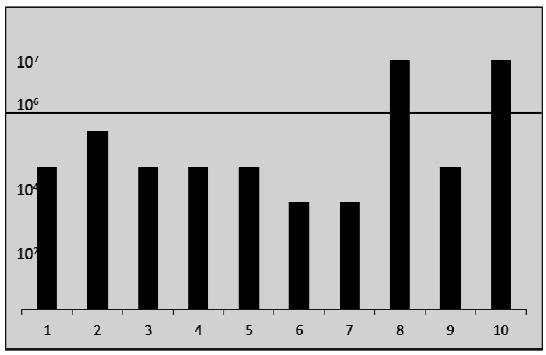

Figure (4) HBV DNA levels in Immune escape phase

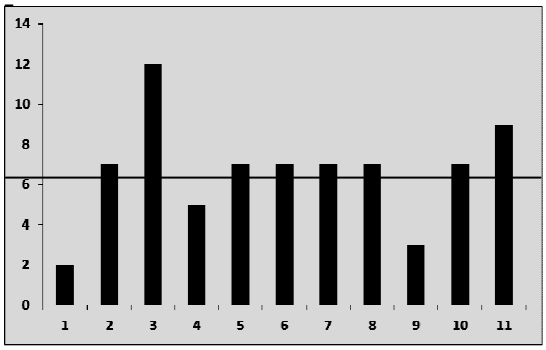

Figure (5) Histologic activity index (HAI) in Immune phase

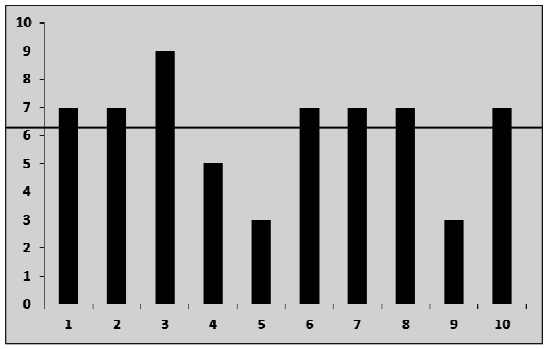

Figure (6) Histologic activity index (HAI) in tolerant Immune escape phase

4. Discussion

This is a very small cross sectional survey. In Bangladesh, prevalence of HBsAg in pregnant women is 3.5 %. This indicates perinatal transmission plays major role in transmission of virus in young age group. Horizontal transmission by common practices like circumcision, hair cutting in saloon, ear piercing by non-trained persons, dental treatment by quacks may have a role. The study revealed some interesting findings like contrary to normal belief of Immunotolerant stage with HBsAg positivity, HBeAg positivity, high HBV-DNA levels in young persons, Immune escape/Reactivation stage with HBsAg positivity, HBeAg negativity, anti HBe positivity, low HBV-DNA levels also seen in teenage patients. This is probably due to acquisition of virus in very childhood. This study showed low mean ALT and HBV DNA levels in group B. Mean histologic activity index (6.63 vs 6.2) and fibrosis scores (1 vs 1.2) were low and was similar in both groups. 8 patients (72.72 %) in group A, 7 patients (70 %) in group B had necro-inflammation 7 and above. Stage 3 fibrosis (F3)was present in 1 patient each group i.e. (9-10 %). The study was consistent with result of other studies. Progression to liver fibrosis seems to be proportional to age at infection. ALT activity appears to be higher in children with significant (S2-S4) fibrosis. Spontaneous hepatitis B early antigen seroconversion is apparently related to the shorter length of infection and higher ALT activity [8]. Another study done in India involving 116 children aged <15 years with chronic hepatitis B reveal a strong positive correlation between AST, ALT, HBV DNA and histologic severity of disease (HAI > or = 4, fibrosis > or = 2). Also median HBV DNA levels was significantly higher in HBeAg positive

compared with HBeAg negative groups. 74 % mothers had evidence of past or present HBV infection [9]. Study from China which was done on adult population revealed at least 23.7 % of chronic hepatitis B patients with persistently normal ALT (PNAL), regardless of what their HBeAg statuses or viral load levels had significant pathological changes. They recommend liver biopsy in CHB patients with PNAL, especially those older than 40 years and with a higher ALT within (0.76-1) × ULN [10]. Another study done in chronic hepatitis B and inactive carriers with normal alanine aminotransferase levels reveal severe fibrosis (F3-4) in HBeAg negative hepatitis and those older than 40 years. The study revealed severe fibrosis was present in 21.1 % in those older than 40 years but 7.7 % in patients younger than 18 years [11]. Another study from Bangladesh involving 36 young individuals up to 20 years of age with HBeAg negative chronic hepatitis B revealed significant necro-inflammation (HAI-NI >3) in 56 % and significant hepatic fibrosis (HAI-F $\geq$2) 17.6 % of patients. Study also revealed serum ALT (cut off 42 U/L) was raised in 38.2 %, while high HBV DNA load (>10^5 copies/ml) was observed only in 26.5 %. This study, shows a significant percentage of HBeAg negative chronic hepatitis B patients have high HBV DNA load and more importantly considerable hepatic damage [12].

5. Conclusion

This is a very small study, however it is an eye opener. Though HBeAg positive is more common in younger population which presents mainly in Immune tolerant phase. HBeAg negative variety – which represents Immune escape/reactivation phase, is not infrequent in teenagers. Commonly Immune escape/reactivation phase is seen in adults and elderly CHB patients. Early loss of immune tolerant phase may be the cause but this form of chronic hepatitis B is difficult to treat and presents with advanced liver disease if not diagnosed and followed up in early stage. We commonly delay treatment in group A and B because of not fulfilling the criteria of treatment. So proper evaluation of these patients is needed to start treatment. Characterisation and histologic evaluation need. Bangladesh has incorporated hepatitis B vaccination to Expanded Program of Immunization (EPI) program since 2004. It is certainly a welcome step but the schedule may need to be reviewed. Immunizing babies at 6 weeks of life with the first dose of vaccine will leave many at risk babies unprotected in their neonatal period when they need it most. 1.2-3.5% of the pregnant ladies in Bangladesh are HBsAg positives & 22-38% of them are also HBeAg positives. Therefore, delaying vaccination for the first 6 weeks will put 70-90% babies at risk of acquiring perinatal infection [13]. Immunizing them in the first twenty-four hours of birth is conceivably the best approach. So other than treatment strategies early vaccination of new born babies is needed to combat HBV infection. Change in vaccination strategy, screening of young generations for HBsAg, safe blood transfusion, safe disposal of infected syringes and treatment of HBV infected persons are present demand to contain vertical and horizontal transmission.

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