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Children with Chronic Hepatitis B in the US and Canada

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Abstract

Objectives—To test the hypothesis that children with chronic hepatitis B (CHB) living in the US and Canada would also have international origins and characteristic hepatitis B virus (HBV) genotypes and laboratory profiles.

Study design—Clinical characteristics of children enrolled in the HBRN were collected from 7 US and Canadian centers.

Results—Children (n=343) with an age range of 1.0 – 17.8 years were enrolled; 78% of the children were Asian, 55% were adopted and 97% had international origins with either the child or a parent born in one of 31 countries. The majority had hepatitis B virus (HBV) genotype B (43%) or C (32%), and the remainder had genotype A (5%), D (16%), E (4%), or multiple (<1%). Children with genotype B or C were Asian (98% and 96%), more consistently hepatitis B e antigen (HBeAg) positive (95% and 82%), had higher median HBV DNA levels (8.2 and 8.3 $\log_{10}$ IU/mL), and less frequently had elevated alanine aminotransferase values (43% and 57%)

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compared with children with other genotypes. The percentage of HBeAg positivity and of those with HBV DNA ≥6 $\log_{10}$ IU/mL declined with age.

Conclusions—The majority of children in the HBRN have HBV genotypes which reflect their international origins. Clinical and laboratory data differ substantially by patient age and HBV genotype. Use of these data can help drive the development of optimal strategies to manage and treat children with CHB.

Keywords

hepatitis B DNA; hepatitis B E antigen; viral genotype; international adoptees

Chronic hepatitis B virus (HBV) infection frequently results in significant liver disease, with up to 25% of individuals developing cirrhosis and/or liver cancer[1–2]. The burden of morbidity and mortality is particularly significant for those who are infected at birth. The introduction of universal newborn vaccination against HBV has resulted in a dramatic decline in the rates of perinatally-acquired chronic HBV infection and hepatocellular carcinoma (HCC).[3] In the US, infant and childhood HBV vaccination has resulted in a striking decrease in new cases of acute hepatitis B in the pediatric population.[4] In contrast the majority (95%) of newly identified chronic HBV cases in adults occur in individuals who have emigrated from areas of high HBV endemicity.[5] It is estimated that 53,800 chronically HBV infected individuals emigrated from their country of origin to the US each year between 2004 and 2008[5]. The impact of immigration on rates of HBV in US children and their clinical and virological characteristics are not well defined. In contrast the clinical and demographic features of young HBV-infected subjects residing in the Middle East and Asia are well described [6–10].

HBV is divided into at least 8 genetically distinct genotypes that are concentrated geographically. It is increasingly recognized that HBV genotypes induce different responses by the host immune system and have differing rates of disease progression, risk of HCC and response to therapy. Development of effective strategies for monitoring and treating chronic HBV in children in the US and Canada depends on an understanding of virological and clinical aspects of this chronic infection[11]. This is of particular importance given the unique and diverse mix of immigrants among HBV patients in the US and Canada, and the accompanying diversity of HBV genotypes in this population.

In addition to viral genotype, patient age is known to significantly impact the rate of disease progression. Chiu et al[12] reported that 78% of Taiwanese children who were positive for hepatitis B envelope antigen (HBeAg) lost HBeAg over a 20 year period. Similarly in a Canadian pediatric cohort, there was 50% HBeAg loss by a median of 17.9 years of age [13]. Describing the natural history of the relationship between age and HBeAg loss could provide useful information for assessing the effects of antiviral treatments, particularly because loss of HBeAg is often used as an endpoint in clinical trials.

The aim of this study was to perform a comprehensive cross-sectional analysis of demographic, clinical and virologic characteristics among a large group of HBV-infected children living in the US or Canada who were enrolled in the multi-center pediatric cohort

study of the Hepatitis B Research Network (HBRN) of the National Institute of Diabetes, Digestive and Kidney Diseases. Of particular interest were comparisons by viral genotype and age. Given the large proportion of adopted children enrolled in the cohort, the entire family of each child was also characterized. Potential differences between children living in Canada (one-third of the cohort) versus the majority living in the US were also assessed.

METHODS

The HBRN is described in detail in a study of the adult cohort[14]. The goal of the network is to facilitate and conduct clinical, scientific, epidemiological and therapeutic research in acute and chronic HBV infection in both adult and pediatric participants who reside in the US or Canada. The HBRN consists of 13 clinical consortia. Each consortium is comprised of 1–3 clinical centers resulting in 21 adult and 7 pediatric clinical sites in the US and Canada, a Data Coordinating Center, and an Immunology Laboratory. The seven participating pediatric sites are in the US states of California, Maryland, Minnesota, Missouri, Texas, and Washington, and Ontario, Canada.

At the inception of the HBRN, members of the Pediatric Subcommittee worked in conjunction with the adult hepatology sites of the Steering Committee so that similar information would be collected for both the adult and pediatric cohort studies. Depending on the data being collected, forms were completed by the investigator, the research coordinator, or by the patient or caregivers with assistance from the coordinator or interpreter if necessary.

Screening and enrollment as of March 2014 for the Pediatric Cohort Study of the HBRN are summarized in Figure 1 (available at www.jpeds.com). Of the 88 who were eligible but not enrolled, 7 were pending enrollment, slightly over 50% refused, and the remainder did not enroll because of language barriers, inability to comply with follow-up, were not approached for participation (reason not specified), or for other reasons (ward of state [n=1], no parent [n=1], unknown [n=1]). No study activities were conducted until the legal guardian(s) had signed the informed consent. Children ≥12 years of age signed an assent form per the requirements of the individual Institutional Review Boards. Interpreters were provided for non-English speakers. Informed consent in writing was obtained from each caregiver. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the appropriate institutional review committee at each study site and at the data coordinating center.

Screening and Baseline Visits

Inclusion criteria were as follows: (1) ≥6 months and < 18 years of age; (2) hepatitis B surface antigen (HBsAg) positive; and (3) written informed consent/assent. Patients were excluded from the Pediatric Cohort Study if there was: (1) history of hepatic decompensation; (2) history of HCC; (3) history of liver transplantation; (4) known human immunodeficiency virus co-infection; (5) current antiviral therapy for HBV; (6) inability/unwillingness to return for study visits; or (7) history or other evidence of severe illness or other medical or social condition that would make the subject, in the opinion of the investigator, unsuitable for the study. The baseline evaluation included a detailed medical

history, physical examination, and laboratory tests. Information on risk factors for HBV infection, family history of HBV, prior treatment of HBV, recent imaging tests and results, medical comorbidities, health behavior, and socio-economic status was recorded. Consent was obtained for research purposes for whole blood to obtain serum and plasma and lymphocyte DNA for genetic testing. Blood samples for standard clinical care were also obtained.

Laboratory analyses

Two central virology laboratories were contracted for performing assays of quantitative HBV DNA, HBsAg and HBeAg levels, HBV genotype, and molecular variants. HBV DNA levels were determined using a real-time polymerase chain reaction assay (ROCHE COBAS Ampliprep/COBAS Taqman HBV Test, v2.0, (Pleasanton, Calif). which has a lower limit of detection of 20 IU/mL. Genotyping of HBV was performed by the Centers of Disease Control using mass spectrometry (MALDI-tof) of a 441bp fragment of the S gene, containing the a-determinant[15]. For participants with missing HBV DNA or HBV genotype results from the central laboratories at the baseline visit, results from clinical sites were used for analysis. Alanine aminotransferase (ALT, U/L was recorded from clinical results obtained within 12 months of baseline study visit. HBV DNA (IU/mL), and HBeAg status were tested by a central laboratory. When central laboratory results were unavailable (e.g. due to inadequate sample), the most recent clinical results obtained within 1 year (for HBV DNA) or 2 years (for HBeAg) of the baseline study visit were used. Results of laboratory tests including complete blood counts, liver panel, creatinine, international normalized ratio, alpha-fetoprotein, HBV DNA, HBsAg, anti-HBs, HBeAg, anti-HBe, antihuman immunodeficiency virus, anti-hepatitis C virus, anti-hepatitis delta virus, and autoimmune markers were recorded when obtained for standard care. The Upper Limit of Normal (ULN) for ALT were: ages 6 months to ≤18 months: 60 IU/mL for males and 55 for females; ages >18 months: 40 IU/mL in males and 35 for females[16].

Statistical Analyses

Demographic and clinical characteristics were summarized using descriptive statistics for the overall cohort, and separately by HBeAg status, genotype, and family composition. Continuous variables were presented as means with standard deviation (SD) or medians with 25^{th} and 75^{th} percentiles. Frequencies and percentages were provided for categorical variables. Significance testing of demographic and clinical characteristics according to HBeAg status, genotype, and family composition was also performed. A non-parametric test (Kruskal-Wallis) was used for continuous variables, whereas the chi-square tests or its exact equivalent was used for categorical variables, as appropriate. Clinically relevant cutoffs for HBeAg (positive, negative), ALT (normal, >1xULN) and HBV DNA (<3 $\log_{10}$ IU/mL, 3 to <6 $\log_{10}$ IU/mL, ≥6 $\log_{10}$ IU/mL) were compared across age groups using the Mantel-Haenszel chi-square test. For this descriptive presentation, no adjustment for multiple comparisons was done. P-values less than 0.05 were considered to be statistically significant.

RESULTS

Mean age of the 343 pediatric subjects was 10.4 years with a range of 1.0–17.8 years; 39% were boys and 61% girls (Table I). The majority of subjects (78%) were Asian, and more than half were adopted. 13% had previously received treatment of HB.. Among the 277 with specified mode of transmission, the majority contracted HBV vertically (97%). Although the eligibility criteria allow participants to have either acute or chronic HBV infection, there have been no cases with acute infection enrolled to date.

Demographic and disease characteristics by HBeAg status

Children who were negative for HBeAg were on average 2.7 years older ($p<0.01$) than children who were positive for HBeAg (Table I). The distribution of race differed by HBeAg status ($p<0.01$), with 84% of the HBeAg positive group being Asian compared with 59% of participants who were negative for HBeAg. Fewer than 10% of the HBeAg positive group had previously received HBV treatment compared with nearly one-third of those who were negative for HBeAg ($p<0.01$). Participants who were positive for HBeAg had higher median serum HBV DNA and ALT levels compared with participants who were negative for HBeAg. Sex, adoption status, mode of transmission, and platelet count did not differ significantly according to HBeAg status ($p>0.05$).

HBV laboratory measures by age

The percentage of participants who were positive for HBeAg decreased with age, from 91% (<5 years) to a low of 62% (≥15 years; $p<0.01$) (Figure 2, A). The percentage with normal ALT levels (<1xULN) was similar across age groups (44–48%, $p>0.05$). Participants who were positive for HBeAg with ALT >1xULN comprised the largest group for all ages, ranging from 54% of those <5 years old to 36% of those ≥15 years old. The percentage of children with HBV DNA ≥6 $\log_{10}$ IU/mL also decreased with age ($p<0.01$; Figure 2, B). Nevertheless, the majority of children in each age group had high HBV DNA, decreasing from 92% to 56% in the youngest and oldest groups, respectively.

Demographic and disease characteristics by genotype

The genotypes of the 230 individuals with available results were: A 5%, B 43%, C 32%, D 16%, E 4%, and <1% (n=1) had multiple genotypes (Table II). Children with genotypes B and C were younger than the other groups, were consistently HBeAg positive, had higher median HBV DNA and more frequently had normal ALT compared with children with other genotypes. Nearly all of those with genotypes B and C were Asian, as compared with 50% of those with genotype D. Only 3 of the 11 with genotype A were Asian (27%) and none of the 10 with genotype E or multiple genotypes were Asian ($p<0.01$).

The predominance of B and C genotypes among those born in the US and Canada, many of whom were born to Asian immigrants, mirrors the genotypes that predominate among those who were born in Asia (Figure 3). In contrast, genotype D was most prevalent in European-born children, and Genotype E was most common in African-born children. In the overall cohort, 119 children were born in China, 49 in Canada, 38 in the United States, 32 in Vietnam, 13 from the Russian Federation, and 13 from India (not shown). The remaining 78

enrollees were born in a total of 27 other countries (1 – 10 children per country). Country of birth was unknown for one child. Among children born in the US or Canada, 26 were born to mothers from Vietnam and 24 to mothers from China; only 9 of this group were born to mothers who were born in the US (n=8) or Canada (n=1). All but two children were residing in the US or Canada. One resided in Africa and one in Ireland; both made annual visits to the US for care.

Comparisons across family composition

More than one-half of the subjects were adoptees (55%; Table III). Mean age was highest in immigrant children living with biological families (12 years), as compared with nonimmigrants and adopted children (mean 10 years) (not shown). The majority of females were adopted (67%). This is in contrast to males, the majority of whom were living with biological families.

The majority of white (79%) and black (61%) children were adopted, whereas half of the Asian (52%) children were adopted. The 29 children born in the Americas (outside of the US/Canada) or Europe were adopted. In addition, about two-thirds of those born in Asia or Africa were adopted. In contrast, only 7% of those born in the US/Canada were adopted.

Among children receiving past treatment for HBV, the majority were adoptees (77%). HBV DNA levels were also associated with family composition; 55 % of the adoptees had high levels vs lower proportions of the immigrant children ($p<0.01$). Family composition was not statistically significantly associated with ALT ($p=0.10$). Genotypes B and D included the largest proportion of adoptees, as compared with other genotypes ($p=0.01$).

US and Canadian cohorts

There were several differences between the US and Canadian cohorts. In the US, 74% of the children were adopted whereas there were only 14% adoptees in Canada ($p<0.01$). A smaller proportion of US participants were Asian (74%) as compared with Canadian (85%) participants ($p=0.02$). In the US, 78% of participants were positive for HBeAg compared with 65% in Canada ($p=0.01$). Children in Canada were older (mean 11.2 years) compared with the US (mean 10.0 years; $p=0.01$). The male:female ratio was ~ 1:1 in Canada as opposed to 1:2 in the US ($p<0.01$), patterns which reflect the higher proportion of females among adoptees combined with the differing proportions of adoptees in the US and Canada.

DISCUSSION

There were a number of key findings in this large, multicenter pediatric cohort observational study: (1) there was substantial HBV genotypic diversity, with the most common HBV genotypes being B and C; (2) over one-half of the children were international adoptees; (3) laboratory profiles varied by genotype; and (4) there was an age-dependent decrease in HBeAg positivity and decline in quantitative HBV DNA levels.

The predominant HBV genotypes in this cohort of children in the US and Canada were genotypes B and C, reflecting the preponderance of Asians in this cohort. However, there were small numbers of children with genotype A or D (mostly from Europe), or E (mostly

from Africa). In adults, genotypes A and B have been associated with better response to interferon than genotypes C and D[17 – 20] whereas the latter-mentioned genotypes may be associated with more severe liver disease and higher HBV DNA levels compared with those with genotype B[18]. Furthermore, there are geographic differences in genotype-phenotype associations. For example, Genotype B is associated with HCC in Taiwan but rarely so in Japan and China[18]. Little has been written about the clinical significance of genotypes in children although there are reports that genotype C may be associated with glomerulonephritis in Chinese children[21].

About one-half of our pediatric cohort was infected with either genotype C or D, genotypes which are associated with the highest risk of HCC among adults. However, the observationthat ~ 20% of European children with HBV experience a change of genotype following HBeAg sero-conversion (a change which had not previously been reported, and has yet to be independently confirmed) emphasizes the need for a comprehensive longitudinal investigation of HBV genotype-phenotype distribution in US and Canadian children [22].

Our findings are in agreement with previous studies that report the rate of HBeAg positivity in older children is lower vs. that of the younger subjects[12, 13]. These findings have important implications for developing appropriate treatment strategies[23] and interpreting results of treatment vs. the natural history of HBV in the pediatric population. For example, the recommendation to focus treatment on subjects who are positive for HBeAg with elevated ALT levels[32]would be 56% of our youngest cohort, but only 36% of those > 15 years of age. Given that this is a cross-sectional study the implications of the loss of HBeAg positivity on clinical outcome are not known. Treatment induced HBeAg loss is predictive of HBsAg loss.[24–27] Loss of HBeAg positivity in adults, described in the REVEAL study, was associated with reduced risk of cirrhosis and HCC over many years of follow up[28]. Only with longitudinal observations will we be able to understand the clinical implications of the loss of HBeAg, for our pediatric HBRN cohort.

The differences between the pediatric and adult enrollees in the HBRN also emphasize the importance of designing age appropriate strategies for both monitoring and treatment. Compared with adults enrolled in the HBRN[14], a higher proportion of the pediatric cohort was female (61% vs. 49%) but the proportion of Asians and immigrants in both pediatric and adult cohorts were similar. However, the prevalence of HBeAg positivity at enrollment was considerably higher in the pediatric cohort (74 vs 26%). The children also had higher median HBV DNA levels at enrollment (8.1 vs 3.6 $\log_{10}$ IU/mL) but only slightly lower percentage with prior treatment (13 vs 14.5 %).

This study had several limitations. The majority of adoptees were female so the status of male adoptees may not be representative. Likewise the number of children with genotypes other than B and C was small. In addition, HBV genotype results were available for only a subset of the cohort (only half, if one were to include those subjects meeting the inclusion criteria who were not enrolled.). Furthermore there were only 7 pediatric sites represented so the genotype distribution might have been different than those we reported had more large urban locales, reflecting different migration patterns, been included. For example New York

State and New York City have a large West African immigrant population as opposed to Minnesota whose African population is largely North African.

Our findings will be useful in understanding the natural history of chronic HBV in this important age group. These findings also have public health ramifications. The American Academy of Pediatrics recommends that all immigrant children be screened for HBV and that if the screening is performed in the country of origin it should be repeated in the US[29]. The current findings corroborate that recommendation. These results also indicate that strategies to monitor and treat HBV-infected children in the US and Canada need to take the effects of genotypic diversity and age into careful consideration. It is not clear how many children in the US and Canada have chronic HBV infection; however, there is a need for better nation-wide data to understand the magnitude of the disease burden in children. Despite the wide availability of the HBV vaccine, HBV in children remains a troublesome reality.

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Abbreviations

ALT	alanine aminotransferase
CHB	chronic hepatitis B
HBeAg	hepatitis B envelope antigen
HBRN	hepatitis B research network
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
SD	standard deviation
ULN	upper limit of normal
US	United States

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Appendix

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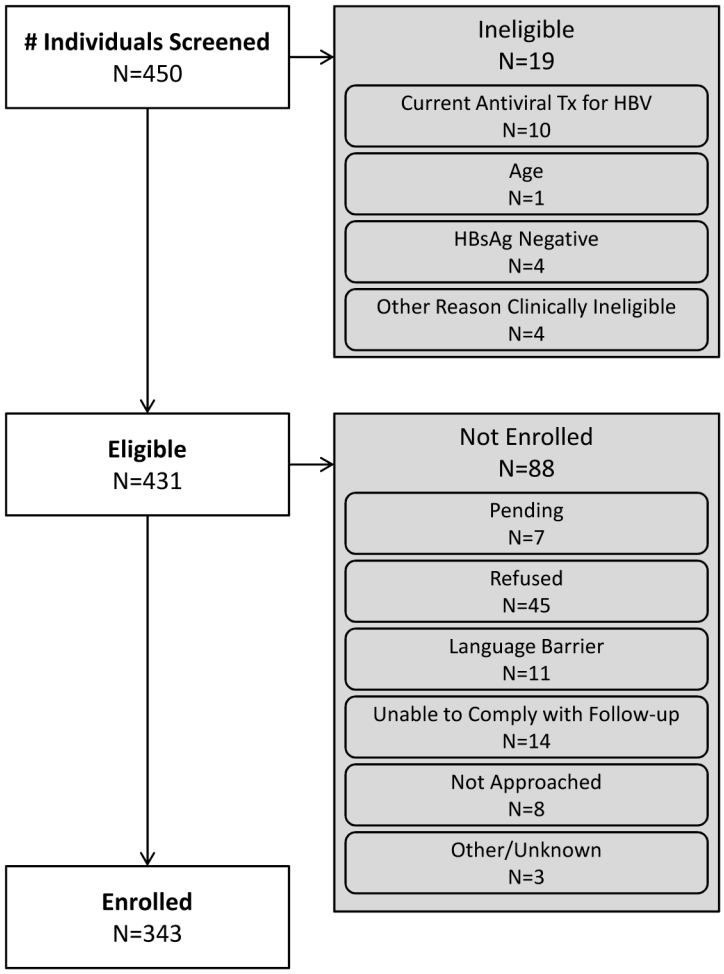

Figure 1.
Enrollment diagram

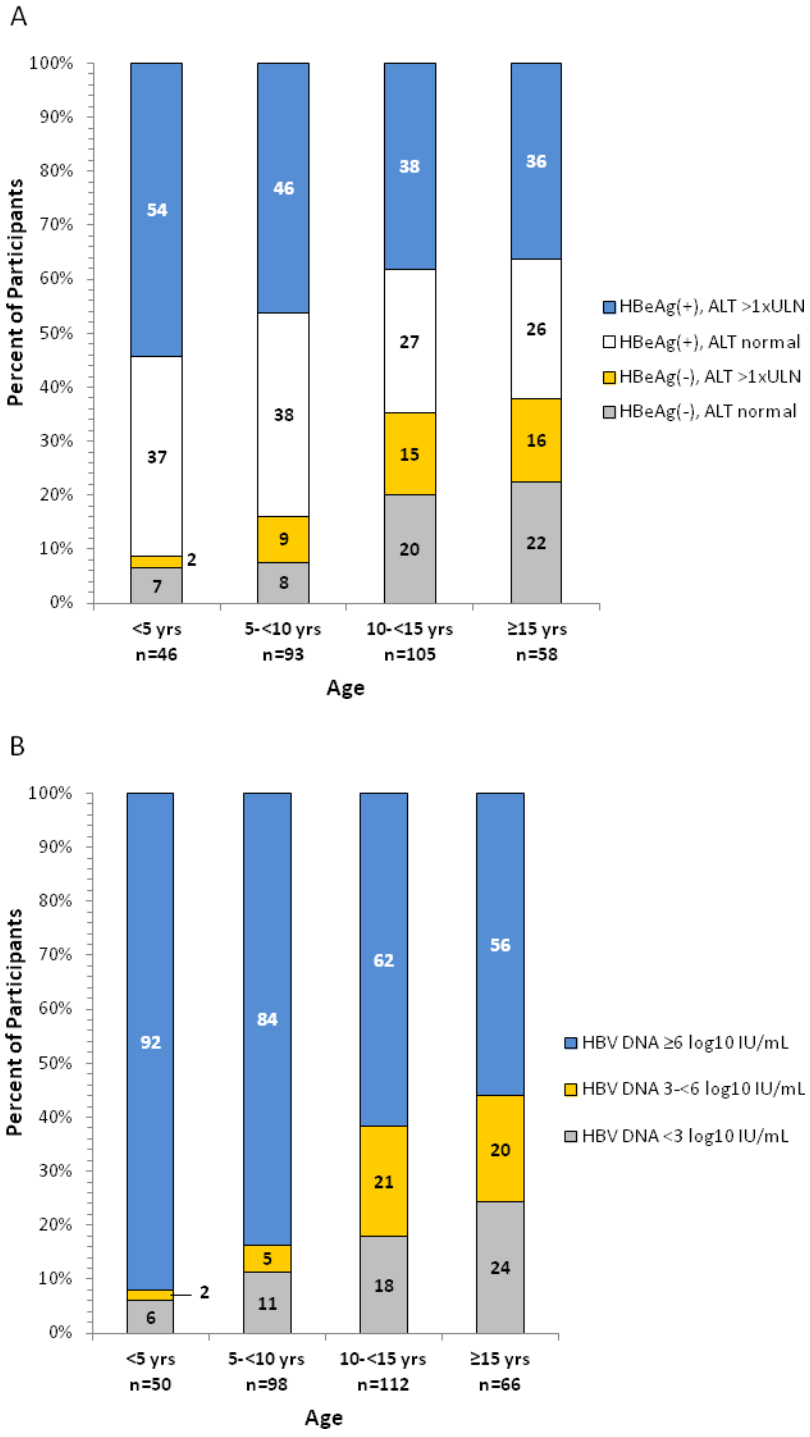

Figure 2.

A, Relationship between age, HBeAg and ALT levels demonstrating an age-related decline in the percent of participants who were HBeAg positive with ALT >1 x ULN and a corresponding increase in those who were negative for HBeAG with normal ALT. B, Relationship between age and HBV DNA levels demonstrating an age-related decrease in

the percent of participants with HBV DNA >6 $\log_{10}$ IU/mL and a corresponding increase in those with HBV DNA <3 and 3 – < 6 $\log_{10}$ IU/mL

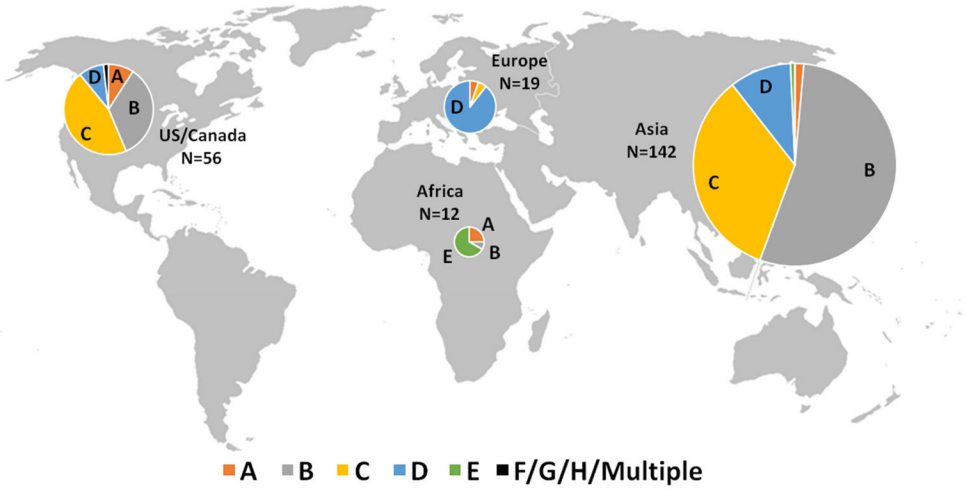

Fig 3.

Pediatric Genotype by Birthplace illustrating a predominance of B and C genotypes among those born in the US and Canada, mirroring the genotypes that predominate among those born in Asia. Genotype D is most prevalent in European-born children, and Genotype E is most common in African-born children.

Table 1

Baseline characteristics by HBeAg status

Characteristic	All N=343	HBeAg(−)[E] N=81 (26%)	HBeAg(+) N=226 (74%)	p-value
Age (yrs)[A]	N=343	N=81	N=226	<0.01
Mean(SD)	10.4 (4.5)	12.4 (3.7)	9.7 (4.5)	
Sex[B]	N=343	N=81	N=226	0.09
Female	210 (61%)	43 (53%)	146 (65%)	
Race[B]	N=341	N=80	N=225	<0.01
White	29 (9%)	19 (24%)	7 (3%)	
Black	36 (11%)	12 (15%)	21 (9%)	
Asian	265 (78%)	47 (59%)	189 (84%)	
Mixed/Other	11 (3%)	2 (3%)	8 (4%)	
Adopted[B]	N=343	N=81	N=226	0.36
	188 (55%)	40 (49%)	125 (55%)	
Ever Received HBV Treatment[B]	N=343	N=81	N=226	<0.01
	43 (13%)	23 (28%)	14 (6%)	
Vertical Transmission[B]	N=277	N=55	N=189	0.66
	269 (97%)	53 (96%)	184 (97%)	
HBV DNA (log_{10} IU/mL)[C]	N=326	N=78	N=217	<0.01
Median(25:75)	8.1 (4.6 : 8.6)	2.5 (1.3 : 3.4)	8.3 (8 : 9)	
≥6 log_{10} IU/mL	234 (72%)	2 (3%)	206 (95%)	
ALT (U/L), Males[A]	N=130	N=36	N=80	0.02
Median(25:75)	42.5 (32 : 59)	38.5 (32.5 : 43.5)	44.5 (34 : 73)	
ALT (U/L), Females[A]	N=204	N=42	N=144	<0.01
Median(25:75)	37 (25 : 49)	29 (19 : 40)	38 (27 : 59)	
ALT x ULN[B,D]	N=334	N=78	N=224	<0.01
≤1 x ULN	152 (46%)	44 (56%)	95 (42%)	
>1 to 2 x ULN	132 (40%)	31 (40%)	86 (38%)	
>2 x ULN	50 (15%)	3 (4%)	43 (19%)	
Platelets (10^3/mm^3)[C]	N=296	N=71	N=199	0.14
Median(25:75)	267 (233.5 : 310)	259 (234 : 310)	274 (239 : 308)	
<160,000/mm^3	12 (4%)	5 (7%)	5 (3%)	

[A] Summarized by N of observed data, and mean(standard deviation) or median(25th:75th percentile)). P-values were based on the Kruskal–Wallis test.

[B] Summarized by N of observed data and frequency (column percentages). Column percentages may not add to 100 due to rounding error. P-values were based on the test or its exact version when appropriate.

[C] Summarized by N of observed data, median (25th:75th percentile), and frequency (column percentages) of categorized values. P-values were based on the Kruskal-Wallis test.

[D] ULN: Upper limit of normal [6 months to <=18 months: 60(M), 55(F); >18 months: 40(M), 35(F)]

[E] Two participants with equivocal results were included in the HBeAg(−) group.

Table 2

Baseline characteristics by genotype

Characteristic N (%)	A 11 (5)	B 99(43)	C 74(32)	D 36(16)	E/Multiple 10(4)	p-value
Age (yrs)[A]	N=11	N=99	N=74	N=36	N=10	<0.01
Mean(SD)	11.9 (4.5)	10.2 (4.6)	9.4 (4.1)	11.9 (4.2)	14.0 (2.9)	
Sex[B]	N=11	N=99	N=74	N=36	N=10	0.14
Female	5 (45%)	71 (72%)	46 (62%)	22 (61%)	4 (40%)	
Race[B]	N=11	N=99	N=72	N=36	N=10	<0.01
White	1 (9%)	0 (0%)	0 (0%)	18 (50%)	1 (10%)	
Black	7 (64%)	1 (1%)	0 (0%)	0 (0%)	8 (80%)	
Asian	3 (27%)	97 (98%)	69 (96%)	18 (50%)	0 (0%)	
Mixed/Other	0 (0%)	1 (1%)	3 (4%)	0 (0%)	1 (10%)	
HBeAg[B,E]	N=9	N=88	N=67	N=35	N=10	<0.01
HBeAg(+)	8 (89%)	84 (95%)	55 (82%)	15 (43%)	3 (30%)	
HBV DNA (log_{10} IU/mL)[C]	N=11	N=95	N=72	N=35	N=10	<0.01
Median(25:75)	7.9 (3.7 : 8.3)	8.2 (7.9 : 8.6)	8.3 (7.7 : 8.8)	4.1 (3.1 : 8.3)	4.4 (3.1 : 8.2)	
≥6 log_{10} IU/mL	7 (64%)	88 (93%)	61 (85%)	12 (34%)	3 (30%)	
ALT (U/L), Males[A]	N=6	N=27	N=28	N=13	N=6	0.20
Median(25:75)	53.5 (38 : 115)	43 (32 : 55)	43 (34.5 : 57)	35 (30 : 41)	73 (32 : 102)	
ALT (U/L), Females[A]	N=4	N=70	N=45	N=22	N=4	0.24
Median(25:75)	88 (37 : 747.5)	33 (25 : 47)	36 (24 : 46)	40 (34 : 48)	45.5 (39 : 55.5)	
ALT[B,D]	N=10	N=97	N=73	N=35	N=10	0.01
≤1 x ULN	3 (30%)	55 (57%)	31 (42%)	16 (46%)	2 (20%)	
>1 to 2 x ULN	3 (30%)	27 (28%)	32 (44%)	18 (51%)	5 (50%)	
>2 x ULN	4 (40%)	15 (15%)	10 (14%)	1 (3%)	3 (30%)	

[A] Summarized by N of observed data, and mean(standard deviation) or median(interquartile range). P-values were based on the Kruskal–Wallis test.

[B] Summarized by N of observed data and frequency (column percentages). Column percentages may not add to 100 due to rounding error. P-values were based on the test or its exact version when appropriate.

[C] Summarized by N of observed data, median (interquartile range), and frequency (column percentages) of categorized values. P-values were based on the Kruskal-Wallis test.

[D] ULN: Upper limit of normal [6 months to <=18 months: 60(M), 55(F); >18 months: 40(M), 35(F)]

[E] Two participants with equivocal results were included in the HBeAg(−) group.

Table 3

Baseline characteristics across family composition

Characteristic	Adopted N=188	Living with Biological Parent(s)		p-value
		Immigrant N=73	Non-Immigrant N=81	
Age[A]	N=188	N=73	N=81	<0.01
<3 yrs	7 (39)	3 (17)	8 (44)	
3 to <8 yrs	59 (63)	11 (12)	23 (25)	
8 to <12 yrs	57 (65)	16 (18)	15 (17)	
12 to <15 yrs	30 (41)	24 (33)	19 (26)	
15 to <18 yrs	35 (50)	19 (27)	16 (23)	
Sex[A]	N=188	N=73	N=81	<0.01
Male	47 (36)	39 (30)	46 (35)	
Female	141 (67)	34 (16)	35 (17)	
Race[A]	N=186	N=73	N=81	<0.01
White	23 (79)	1 (3)	5 (17)	
Black	22 (61)	9 (25)	5 (14)	
Asian	138 (52)	63 (24)	63 (24)	
Mixed/Other	3 (27)	0 (0)	8 (73)	
Place of Birth[A]	N=188	N=73	N=81	Not Tested
US/Canada	6 (7)	0 (0)	81 (93)	
Other North America and South America	5 (100)	0 (0)	0 (0)	
Europe	24 (100)	0 (0)	0 (0)	
Asia	137 (68)	64 (32)	0 (0)	
Africa	16 (64)	9 (36)	0 (0)	
Combined Child-Parent Immigration Status[A,D]	N=185	N=73	N=81	Not Tested
Immigrated to US/Canada	180 (71)	73 (29)	0 (0)	
Born in US/Canada & at least one parent foreign-born	2 (3)	0 (0)	75 (97)	
Participant & both parents born in US/Canada	3 (33)	0 (0)	6 (67)	
Ever Received HBV Treatment[A]	N=188	N=73	N=81	<0.01
	33 (77)	6 (14)	4 (9)	
HBeAg[A,C]	N=168	N=70	N=75	<0.01
HBeAg(−)	40 (49)	30 (37)	11 (14)	
HBeAg(+)	128 (55)	40 (17)	64 (28)	
HBV DNA (log_{10} IU/mL)[A]	N=178	N=69	N=78	<0.01
<3 log_{10} IU/mL	25 (50)	16 (32)	9 (18)	
3 to <6 log_{10} IU/mL	26 (62)	13 (31)	3 (7)	
≥6 log_{10} IU/mL	127 (55)	40 (17)	66 (28)	
ALT[A,B]	N=183	N=72	N=78	0.10
≤1 x ULN	93 (62%)	31 (21%)	27 (18%)	
>1 to 2 x ULN	66 (50%)	32 (24%)	34 (26%)	

Characteristic	Adopted N=188	Living with Biological Parent(s)		p-value
		Immigrant N=73	Non-Immigrant N=81	
>2 x ULN	24 (48%)	9 (18%)	17 (34%)	
Genotype[A]	N=127	N=50	N=52	0.01
A	6 (55)	1 (9)	4 (36)	
B	62 (63)	17 (17)	19 (19)	
C	33 (45)	17 (23)	24 (32)	
D	22 (61)	10 (28)	4 (11)	
E	4 (44)	5 (56)	0 (0)	
Multiple	0 (0)	0 (0)	1 (100)	

[A] Summarized by N of observed data and frequency (row percentages). Row percentages may not add to 100 due to rounding error. P-values were based on the test or its exact version when appropriate.

[B] ULN: Upper limit of normal [6 months to ≤18 months: 60(M), 55(F); >18 months: 40(M), 35(F)]

[C] Two participants with equivocal results were included in the HBeAg(−) group.

[D] Values for immigration status were set to missing for two adopted participants not residing in the US or Canada at the time of enrollment.