Hepatitis B Virus Infection in Children

Recent increases in Hepatitis B virus (HBV) infection prompted us to characterize HBV-infected children in Ireland and to audit management, by reviewing prospectively gathered data. Of 46 children (29 [63%] male), median age at presentation was 6.1 years (range 0.6-17.6), monitoring duration was 22.5 months (range 1-101), 23/46 (50%) were European (including 9 [19.6%] Irish), 15 (32.6%) African and 9 (19.6%) Asian. Acquaintance was vertical (25/46 [54.3%]), horizontal (14/46 [10.9%]), unknown (16/46 [34.8%]). HBV-DNA was >100,000,000 cpm in 30/46 (62.5%) with chronic hepatitis B surface antigen (HBeAg) in 30/46. Transition of monitoring was 22.5 (range 1-101). This study was funded by the European Commission (grant 25-46 (54%), horizontal in 4 (9%) and unknown in 17 (37%). The year of presentation (Figure 1) and the ethnicity of patients, defined by the country of origin of their parents, are shown (Figure 2).

Transmission was vertical in 11/15 children born in Ireland. Antenatal maternal hepatitis status was known in 5/11, 4 of whom had received HBV immune globulin and HBV vaccine follow-up. One infant received HBV vaccine at birth, at 6 weeks and 6 months old but proved HBV-infected at 8 months, representing vaccine failure. Two infants presented with acute symptomatic HBV infection, one with chronic HBsAg and HBV DNA. In both cases, delayed administration of follow-up doses may have compromised vaccine efficacy. Another infant commenced vaccination following delivery, HBsAg being detected on the day of delivery and confirmed 6 weeks later, possibly representing in-utero transmission. The third child received 2 doses of vaccine prior to diagnosis of HBV infection. Two infants, HBAg and HBsAg were detected at 1 month and HBV-DNA at 1 and 3 months, all of which subsequently cleared. Vaccination possibly aided recovery in this infant.

SeroLOGY

Thirty-five patients had HBsAg measured at least twice, at least 6 months apart (of the remaining 11 infected patients, 6/11 had less than 6 months follow-up, 5/11 were lost to follow-up); 32/35 (91%) met the criteria for chronic HBV infection, 1/32 subsequently cleared HBsAg spontaneously. This international adoptee diagnosed at 6 months had marked histological activity, HBsAg negative, pre-core mutant virus with HBV-DNA >100,000,000 cpm (copies per million) at diagnosis. At 18 months there was loss of HBsAg and clearance of viremia at 2 and 3 years of age. HBsAg was detected in 33/46 (73%) patients tested.

HBV-PCR

Quantitative PCR testing for HBV DNA was performed on 32/35 chronic HBV patients. 20/32 (62.5%) patients had >100,000,000 cpm with 11/32 (34.3%) having HBV-DNA >100,000,000 cpm. HBV-DNA was >100,000,000 cpm in 26/32 (81%) patients followed for more than 6 months. 11/46 (24%) patients had HBV-DNA >100,000,000 cpm with a median of 1,400,000,000 cpm (range <100,000 cpm to >100,000,000 cpm). HBV-DNA was >100,000,000 cpm in 10/46 (22%) cases. This increase parallels increases in immigration and international adoption, and Irish emigrants returning to live in Ireland.

Co-infection

Four patients cleared HBsAg spontaneously. Two patients diagnosed with acute symptomatic HBV infection cleared HBsAg, one with carrier status 6 months later. One patient with chronic HBV infection had spontaneous clearance of HBsAg at 4 and 36 months respectively. Two patients have undergone liver biopsy, due to persistently elevated ALT and high HBV DNA titres. The first underwent 2 biopsies, each showed minimal inflammation but without interstitial fibrosis. The second underwent 2 biopsies. His first showed fibrosis grade 3/4 and a single area of bridging fibrosis. A course of interferon alpha-2b was commenced. Liver treatment biopsy showed persistence of fibrosis without progression. No other patient received HBV therapy.

Follow-up

Four patients cleared HBsAg spontaneously. Two patients diagnosed with acute symptomatic HBV infection cleared HBsAg, one with carrier status 6 months later. One patient with chronic HBV infection had spontaneous clearance of HBsAg at 4 and 36 months respectively. Two patients have undergone liver biopsy, due to persistently elevated ALT and high HBV DNA titres. The first underwent 2 biopsies, each showed minimal inflammation but without interstitial fibrosis. The second underwent 2 biopsies. His first showed fibrosis grade 3/4 and a single area of bridging fibrosis. A course of interferon alpha-2b was commenced. Liver treatment biopsy showed persistence of fibrosis without progression. No other patient received HBV therapy.

Co-infection

Screening for co-infection was incomplete: 11/45 patients were screened for HDV: 37/45 for HCV: 28/45 for HBV: 11/45 were screened for all 3 co-infections; 17/45 for 2; 9/45 for 1; and 4/5 were not screened for any co-infection. One patient has HDV or HCV co-infection. One patient has HBV co-infection.

Vaccination

32/46 were tested for HAV susceptibility. Natural immunity was detected in 5. Only 16/27 susceptible patients have been vaccinated. Completion of screening and appropriate HBV vaccination and precaution education was documented in 30/45 families.

Vaccine-preventable cases

Based on our criteria, 10/46 (22%) cases were potentially vaccine-preventable.

Discussion

This study demonstrates that very high viral burdens may be encountered in asymptomatic HBV-infected children, even with normal or mildly elevated ALT. This supports previous studies, that in immune-tolerant patients, transaminases may not be useful indicators of viral activity. These data also confirm that absence of detectable HBeAg does not reflect knowledge of parental status, and corresponding absence of risk to a child; in others, screening was likely overlooked. This audit highlights the need to screen systematically for coinfection and, where screening is not indicated, to document specific reasons. HAV vaccination is recommended for HBV-infected children, yet HAV vaccine was not determined in 28% and vaccination opportunities were missed in 41%. There are limitations to this study, it is likely that there are children living in Ireland at the time of this study, that already have HBV infection but who may not be vaccinated, who have not been referred to these centers. Secondly, we documented several patients in whom the mode of HBV infection was unknown.
transmission was unclear. Transmission was classified as unknown when a reliable history was unavailable, such as when care had been transferred to other institutions. In Ireland in 2006, 11% of reported HBV infections were acute, 82% chronic, and 7% unknown. No acute HBV infections were reported in children under 15 years old in 2006.

Fortunately, HBV infection prevalence remains low in children in Ireland. In 2006, 820 HBV notifications were made. In Ireland, HBV vaccination could have prevented nearly one quarter of childhood cases. Other countries with delayed reporting of earlier cases and delayed referral to tertiary services. Nonetheless, in this study, universal neonatal hepatitis vaccination could have prevented nearly one quarter of childhood cases. Other countries with low HBV endemicity also favour universal HBV vaccination. Vaccination protects safely and effectively against HBV infection. Previous Irish policy was to target HBV vaccination with or without HBV-immunoglobulin to at-risk infants identified by screening during pregnancy and to high-risk groups such as family contacts of HBV-infected patients. This targeted immunization failed to reduce the incidence of new infection in the U.S and was replaced by universal immunization in 1992. The change in Irish policy is to be welcomed.

Pending the development of more effective therapies for HBV infection in children, management of HBV-infected children includes regular monitoring of growth, screening for co-infection, vaccination against hepatitis A, treatment if indicated, and prevention of HBV spread. In this audit, missed opportunities included screening for co-infection, provision of HAV vaccination to HBV-infected children, and HBV screening and vaccination of household contacts. These simple but important measures should not be overlooked. Although Ireland has presently a low rate of HBV infection, universal rather than targeted HBV vaccination programmes are necessary. In this cohort, UNV-HBV could have prevented 22% of cases. UNV-HBV has now been adopted in Ireland, and is consistent with WHO recommendations.

References

Correspondence: KM Butler
The Rainbow Clinic, Our Lady’s Children’s Hospital, Crumlin, Dublin 12
Tel: +353 1 4096338
Fax: +353 1 4096376
Email: Karina.butler@olchc.ie

Comments: <br>