Chronic hepatitis B and C infection in children in New South Wales

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ABSTRACT

Objective: To characterise epidemiological, clinical and laboratory features of children in New South Wales with chronic hepatitis B (HBV) or C (HCV) infections.

Design and setting: Retrospective record review of epidemiological, clinical, laboratory, liver biopsy and treatment data for children (aged < 18 years) referred to tertiary referral paediatric and refugee clinics in NSW with chronic HBV or HCV during 2000–2007; and comparison with NSW Health notification data for the same period.

Main outcome measures: Numbers and characteristics of referred children with HBV and HCV, and notifications to NSW Health.

Results: During 2000–2007, 79 children with chronic HBV and 29 with HCV infection were referred to specialist clinics, while 930 children with HBV and 777 with HCV infection were reported to NSW Health. Most of the referred children with HBV were born overseas, while most with HCV were born in Australia to mothers with a history of intravenous drug use. Of the 79 HBV-infected children, 56 were e-antigen positive. Most HCV-infected children (23/29) had alanine aminotransferase levels ⩽ 2 times the upper limit of normal, and more than half of those who had genotype determined had type 2 or 3. Fibrosis was evident in liver biopsies performed for both HBV and HCV.

Conclusions: Although advanced liver disease was uncommon in children referred with HBV or HCV infection, a large number of infected children in NSW were not referred for specialist medical care, indicating that opportunities to intervene early in the natural history of these infections, particularly HCV, are being missed.

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Chronic hepatitis B (HBV) and hepatitis C (HCV) infections cause significant morbidity and mortality through sequelae such as liver fibrosis, cirrhosis and hepatocellular carcinoma. Together, they are the most common indication for adult liver transplantation in Australia.[1] Antiviral therapy is the standard care for adult patients with HCV infection, preventing progression to end-stage disease, and is used in patients with HBV who meet specific criteria.[2] Treatment of children can be as effective as in adults, particularly for HCV.[3] However, antiviral therapy for HCV is not currently approved in the Australian Pharmaceutical Benefits Scheme for those under 18 years of age, thus restricting access to the medications. Chronic HBV or HCV infection in children is usually asymptomatic and may remain undetected, although significant liver disease can occur.[4,5]

There are few published data describing the pattern of chronic viral hepatitis infection in children in Australia. Furthermore, in New South Wales, there are no specific services for care and treatment of these children, in contrast to the adult services available. Here, we describe the epidemiological, serological and biochemical features of a group of children referred to tertiary paediatric clinics in NSW with HBV and HCV infections. We also sought to compare referral numbers with notifications to NSW Health during the same period, and to determine what services are available outside NSW for children in Australia with chronic viral hepatitis.

METHODS

Databases of paediatric gastroenterology, hepatology, infectious diseases and refugee clinics in NSW were searched, and charts of children (aged < 18 years) with HBV or HCV infection during 2000–2007 were reviewed. Patients were defined as having chronic HBV if they were surface antigen (HBsAg)-positive on two occasions 6 months apart. HBV e-antigen (eAg) and e-antibody (eAb) status at referral were recorded. HCV infection was defined as being anti-HCV-positive and RNA-positive on polymerase chain reaction (PCR) testing. HBV and HCV viral loads (quantitative PCR), HCV genotype and liver function results at presentation were recorded. Demographic details (sex, age at referral, country of birth) were also recorded, as well as the likely mode of infection determined from the history provided, results of liver biopsies, and details of antiviral therapy. Likely mode of infection was deemed to be vertical if the patient's mother had a clear history of infection, horizontal if she was known not to be infected, or unclear if this information was not recorded. For HBV cases, any record of neonatal prophylaxis with hepatitis B immunoglobulin and vaccination was noted.

We also reviewed data from the NSW Health Notifiable Diseases Database on all patients aged < 18 years with HBV or HCV who were diagnosed during 2000–2007. Case definition in this database was the detection of HBsAg or HBV DNA for HBV infection, and detection of anti-HCV antibody or HCV RNA for HCV infection, in a patient not previously demonstrated to have evidence of HBV or HCV, respectively. Children less than 18 months of age with anti-HCV antibody alone were excluded because it could not be determined from the available information whether this reflected maternal antibody.

Paediatric gastroenterologists and hepatologists in each of the other Australian states were contacted to determine whether a specific service for children with chronic viral hepatitis existed in their state.

The project was approved by all relevant ethics committees.

RESULTS

During the 8-year period, 79 children with chronic HBV infection and 29 children with chronic HCV infection were referred to paediatric gastroenterology, hepatology, infectious diseases and refugee clinics in NSW.

Hepatitis B

Characteristics of the 79 patients with HBV infection are summarised in Box 1. Fifty-one patients were male, and the mean age at referral was 9.1 years (range, 1–17 years). Most were refugees born in Africa or migrants from Asia. Half of the patients born in Australia or New Zealand had parents who were both born overseas. Vertical transmission (38/79) was more common than horizontal transmission (10/79), but the mode of transmission could not be determined for 31 patients. Seven patients developed HBV infection despite a history of receiving neonatal vaccination and hepatitis B immunoglobulin at birth. Apart from hepatomegaly in one patient

1 Characteristics of 79 patients with hepatitis B (HBV) infection

	Number
Sex	
Male	51
Female	28
Birthplace	
Africa	39
Asia	23
Australia or New Zealand	15
Middle East	2
Serology	
eAg+/eAb–	56
eAg+/eAb+	4
eAg–/eAb+	18
Unknown	1
ALT	
Normal (< 50 U/L)	46
1–2× ULN	16
> 2× ULN	14
Unknown	3
Likely acquisition	
Vertical	38
Horizontal	10
Unclear	31

eAg = HBV e-antigen. eAb = HBV e-antibody.
ALT = alanine aminotransferase.
ULN = upper limit of normal. ◆

and splenomegaly in another, all other patients had normal results of a gastroenterological examination.

There was only one patient for whom eAg/eAb status was not known. Most (56/79) were in the immune tolerant eAg-positive/eAb-negative phase of infection (Box 1). Most of these patients had high viral loads (median, 1.7×10^6 IU/mL), with either normal or slightly raised alanine aminotransferase (ALT) levels. Eighteen patients had undergone eAb seroconversion and had cleared eAg. These patients had lower viral loads and ALT levels, consistent with suppressed viral replication (data not shown). Four patients were positive for both eAg and eAb at presentation. One patient out of the 56 who were initially eAg-positive/eAb-negative had spontaneous seroconversion and became eAg-negative with a low viral load during follow-up. No patients were eAg-negative/eAb-positive with a high viral load.

Liver biopsy was performed on eight patients during the study period because of persistent elevation in transaminase levels, to assess for the degree of inflammation and fibrosis, and for consideration of possible therapy. Two patients had bridging fibrosis evident on biopsy, but none had cirrhosis. Three had mild and two had moderate necroinflammatory activity (by Ishak grading).[6]

Three patients had been treated with antiviral medication for chronic HBV infection. One was treated initially with lamivudine because of immunosuppression from chemotherapy for malignancy, later changed to adefovir due to lamivudine resistance, and has since seroconverted. Another patient developed acute HBV infection (probable horizontal transmission) after cardiac transplantation and received lamivudine, with the subsequent addition of adefovir due to a precore mutant flare, and currently has a low viral load and an ALT level 1–2 times the upper limit of normal. The third patient had commenced treatment with lamivudine in another state, the indication being chronic elevation in ALT and fibrosis on liver biopsy. This patient was lost to follow-up.

Hepatitis C

Characteristics of the 29 patients with HCV infection are summarised in Box 2. Again, there was a male predominance, but most patients were born in Australia. The mean age at referral was 7.8 years (range, 1–14 years). All patients were asymptomatic and none had clinical signs of chronic liver disease at referral.

Of 19 children who had HCV genotyping, eight had genotype 1, and 10 had genotypes 2 or 3. The one patient with genotype 4 was born in the Middle East. Most patients had normal or only mild elevations in ALT levels at their first visit. Five patients had an ALT level greater than two times the upper limit of normal. Despite this, most patients had high viral loads (median, 1.3×10^6 IU/mL).

Twenty-four of the 29 children were thought to have acquired the infection vertically, based on a history of maternal infection. Two of these children also had vertically acquired HIV infection. In 16 of the 29 vertically acquired HCV cases, there was a history of maternal injecting drug use. Two patients whose mothers were not infected with HCV were thought to have acquired the infection from infected blood products: one had a transfusion overseas, and the other in Australia in 1990. For three children, the mode of acquisition was either unknown or not recorded.

2 Characteristics of 29 patients with hepatitis C infection

	Number
Sex	
Male	17
Female	12
Birthplace	
Australia	24
Overseas	3
Unknown	2
Genotype	
1	8
2	1
3	9
4	1
Unknown	10
ALT	
Normal (< 50 U/L)	9
1–2× ULN	14
> 2× ULN	5
Unknown	1
Likely acquisition	
Vertical	24
Horizontal	2
Unclear	3

ALT = alanine aminotransferase.
ULN = upper limit of normal. ◆

Four patients had liver biopsies performed during the study period. The indication in three cases was persistent elevation in liver transaminase levels, while the other biopsy was performed for clinical suspicion of cirrhosis in a patient co-infected with HBV, with a cardiomyopathy secondary to previous treatment for malignancy. This patient had cirrhosis but was not treated after becoming HCV RNA-negative soon after the biopsy. Of the other three patients who had biopsies, two had mild fibrosis and one had no fibrosis. All biopsies had at least mild necroinflammatory activity.

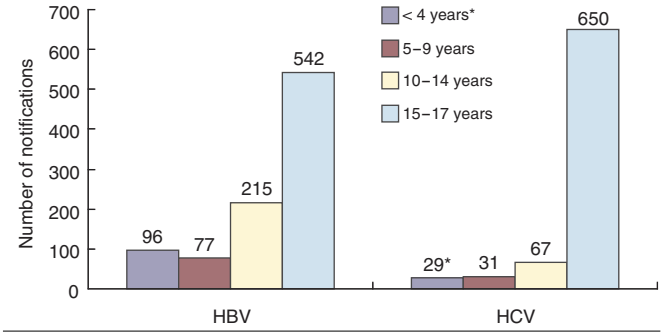
One patient was successfully treated with interferon and ribavirin shortly after transitioning to adult services. No other patients have been treated. Two patients became RNA-negative spontaneously during follow-up.

Public health notifications

Notifications to NSW Health from 2000 to 2007 of children with HBV and HCV infec-

tion are shown in Box 3. During this period, there were 930 HBV notifications for children aged < 18 years and 777 HCV notifications in children aged between 18 months and 18 years. While the 15–17-years age group had the most notifications, 388 children aged less than 15 years with HBV and 127 children aged between 18 months and 15 years with HCV were identified during the 8-year period.

3 New South Wales Health notifications for hepatitis B (HBV) and C (HCV) in children aged < 18 years, 2000–2007, by age group



* For HCV, the < 4-years age group excludes children aged < 18 months. ◆

Interstate services

Our enquiries found that there are no coordinated services for children with chronic viral hepatitis in any Australian state or territory. Children with chronic HBV do not receive antiviral therapy routinely. Children with chronic HCV are not routinely treated in any state except Victoria, where a small number of patients have accessed medication from the manufacturer on a compassionate basis (W Hardikar, Head of Hepatology, Royal Children's Hospital, Melbourne, personal communication).

DISCUSSION

We found that most children referred to tertiary children's hospitals in NSW with chronic HBV infection were born overseas, while most of those with HCV are Australian-born, often to mothers with a history of injecting drug use.

Hepatitis B

Most of the children with HBV infection were either refugees or migrants, or children of refugees or migrants. As refugees are often screened after arrival in Australia, there will be an ascertainment bias in this group. The mode of transmission was unclear for almost 40% of children. Almost half of the Australian-born children had apparently received neonatal prophylaxis with both vaccination and immunoglobulin. These measures have an efficacy of between 70% and 100% in preventing vertical transmission from an eAg-positive mother, depending on her viral load.[7] Our patients in whom this apparently failed underline the need for close follow-up of infants who receive prophylaxis. While most had biochemical evidence of hepatitis, advanced liver disease was uncommon and very few had received treatment.

Age at infection is an important factor in the natural history — children infected vertically or within the first 5 years of life have higher rates of chronic infection (25%–30%) than those infected later in life (5%–10%).[8] Similarly, eAg seroconversion rates vary from 2%–5% per year in young, vertically infected children[9] to up to 70%–80% of horizontally infected older children by age 20.[10] The dominant mode of transmission to children varies by geographical location, with higher rates of horizontal infection in Africa than in eastern Asia, where vertical transmission is most common.[11] These differences may be explained by different HBV genotypes.[12] The mix of geographical origins and differing modes of infection in our group of patients may thus result in varied natural histories.

Cirrhosis occurs in around 20% of adults with chronic HBV infection over a 20-year period[13] and is a precursor to hepatocellular carcinoma. About 4% of horizontally acquired HBV infections in childhood progressed to cirrhosis in one study spanning 29 years,[14] although half of these patients developed hepatocellular carcinoma. In Taiwan, where vertical transmission is common, the annual incidence of cirrhosis in young eAg-positive adults was found to be 2.4%.[15]

Development of progressive liver fibrosis is generally associated with prolonged elevation of ALT levels,[16] but can develop in those with normal ALT levels.[5] Those who have seroconverted can also experience reactivation with either eAg-positive or eAg-negative chronic hepatitis, resuming the risks of increased infectivity and progression of liver disease.[17] These features of HBV infection mandate long-term follow-up for disease progression, with biopsies and therapy if necessary.

Treatment of HBV in children is focused on those who are shown to be developing significant, irreversible liver damage on biopsy.[3] The decision to treat is difficult because of uncertainty about the required length of therapy — when it is ceased, viral loads often rebound. Also, the higher spontaneous eAg seroconversion rate in children, the risk of resistant mutants arising, side effects of medications, and the relatively long lead time from infection to the development of serious liver disease make treatment decisions complicated. Based on paediatric trials, the best evidence for efficacy exists for interferon α-2b,[18] lamivudine,[19] and, more recently, adefovir.[20] However, there is also evidence that there may be less response to antiviral therapy in younger children.[20]

Hepatitis C

In contrast to the patients with HBV, those with HCV infection were mostly Australian-born and acquired infection vertically, typically from mothers with a history of injecting drug use. Few had evidence of significant liver disease, although about half of the patients who had HCV genotyping had genotypes 2 or 3, which have a "cure rate" of greater than 80% with antiviral therapy.[3]

The natural history of paediatric HCV infection is still being elucidated. Around 10%–20% of adults progress to cirrhosis within 20 years of infection.[21] One paediatric cohort study suggests that 8% will clear HCV spontaneously within 10 years, and 1.8% will progress to cirrhosis over the same period.[22] Clearance was more likely with vertically infected children and those with genotype 3, while cirrhosis was more likely with genotype 1 or persistently elevated ALT levels.[22] Rates of histological bridging fibrosis (a precursor to cirrhosis) vary from 4% to 22% in studies, probably related to different genotypes and modes of acquisition.[4,23] It is likely that many of these patients will progress to cirrhosis in adulthood; however, decompensated cirrhosis has been described in children.[22]

The standard first-line treatment for HCV is pegylated interferon α combined with ribavirin, which achieves a sustained virological response (undetectable HCV RNA 24 weeks after stopping therapy) in over 40% of adults with genotype 1 and around 80% with genotypes 2 or 3.[24] Similar results have

been achieved in paediatric trials.[25] Treatment of our group of patients could eliminate chronic HCV infection in a significant proportion, sparing them considerable morbidity, and possibly mortality, later in life. There would also be a health expenditure saving, as well as psychosocial benefits for the individual who would no longer be burdened by the social stigma of the disease. To date, none of our patients have been treated because of a lack of access to medication and insufficient clinic resources to enable treatment.

Public health notifications

We found a major discrepancy between the number of children seen in tertiary referral centres and the number of cases notified to NSW public health units for both HBV and HCV, suggesting many patients are not receiving adequate medical follow-up. The referred children with HBV and HCV account for only 8.4% and 3.7%, respectively, of all notifications in children aged < 18 years during the study period. Even when 15–17-year-olds (who may imminently transition to adult services or be followed by programs within NSW Justice Health) are excluded, referred patients account for only 20.1% and 22.8% of notifications for HBV and HCV, respectively. In addition, without a concerted program to screen at-risk children, there are likely to be more infected children who have not even been tested.

We acknowledge that both the clinic and public health data may include some patients with acute HBV or HCV, and that different case definitions may account for some of the discrepancy between the two, but we suggest this would only have a small effect, if any. We do not believe that a child with a diagnosed acute infection would be less likely to be referred to any of the clinics than a child with chronic infection.

Current literature supports treatment of children with chronic HCV infection, particularly for genotypes 2 or 3. Because of lower response rates, uncertain length of treatment and risks of resistance, treatment of chronic HBV infection should be more selectively applied, depending on individual clinical, laboratory and histopathological circumstances. With no coordinated care and treatment services in place for these children throughout Australia, we are missing important opportunities to prevent significant morbidity, mortality and health care expenditure in adulthood. Appropriate follow-up of infants who receive HBV prophylaxis is essential and could be achieved by such a service, working closely with the state health department.

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COMPETING INTERESTS

None identified.

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