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ORIGINAL ARTICLE

Childhood hepatitis C virus infection: An Australian national surveillance study of incident cases over five years

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Aim: An estimated 1.1% of Australian adults are infected with hepatitis C virus (HCV). Many develop chronic liver disease, and some develop liver failure or hepatocellular carcinoma. HCV infection in Australian children is poorly defined. We aimed to determine the reported incidence, clinical and epidemiological features of newly diagnosed HCV infection in Australian children presenting to paediatricians.

Methods: We undertook prospective active national surveillance, using the Australian Paediatric Surveillance Unit, of incident HCV cases in children aged <15 years between 1st January 2003, and 31st December 2007.

Results: There were 45 confirmed cases of newly diagnosed HCV infection over five years (<1 per 100 000 children aged <15 years per year). Median age at diagnosis was 2.9 years. Positive maternal HCV serostatus was the most frequent reported risk factor for HCV infection in children (40/45). Three children (all aged > 14), were exposed through their own IV drug use. No children were co-infected with HIV and only one child was co-infected with HBV. All children were asymptomatic at diagnosis, although many had minor elevations in liver transaminases. Many clinicians reported difficulties with follow-up.

Conclusions: Childhood HCV infection is uncommon in Australia, although our data likely underestimate the incidence. Only a small number of children aged <18 months was identified, despite known perinatal exposure. Opportunistic investigation of children at risk for HCV, improved education regarding vertical transmission for health care providers, and increased coordination of childhood HCV services are required to improve recognition and management of children with HCV.

Key words: Australia, child, epidemiology, hepatitis C, vertical transmission.

What is already known on this topic

1 Childhood HCV is most commonly acquired through vertical transmission.
2 Australian data on childhood HCV is poorly defined.
3 New antiviral therapies are better tolerated and show greater efficacy for HCV clearance.

What this paper adds

1 Childhood HCV infection in Australia is uncommon and likely unrecognised due to missed opportunities for screening of HCV exposed infants.
2 Maternal HCV seropositivity was the most common risk factor for childhood infection.
3 High risk behaviour (tattoos, and IV drug) in children is another important source of HCV infection.

The global prevalence of hepatitis C Virus (HCV) infection is estimated to be 3% with approximately 3–4 million new infections each year.[1] In Australia approximately 1% of the adult population are infected.[2] Infection is via blood to blood contact, and since the introduction of blood donor screening in Australia between 1989–1990 the most common infection route in adults is through sharing needles and injecting paraphernalia.[3] Infection in children is typically through perinatal transmission by women who are HCV RNA positive at delivery. The overall risk of vertical transmission is approximately 5% although this varies according to maternal risk factors, such as maternal co-infection with human immunodeficiency virus (HIV),[4,5] maternal history of injecting drug use[4,6,7] and prolonged rupture of membranes.[8] The evidence regarding high maternal HCV viral load and mode of delivery is conflicting and inconclusive.[7,8] Similarly there remain many gaps in our understanding of childhood HCV infection.

The natural history of HCV infection in children is not fully described. Chronically infected children are usually asymptomatic, having normal to mildly elevated transaminases

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irrespective of the mode of HCV acquisition.[9,10] HCV persistence has been reported in between 80–90% of children.[9,11] Spontaneous clearance of HCV is reported in up to 27% of perinatally infected infants, usually occurs by school age, and is highest in children infected with HCV genotype 3.[12] Histological assessment of liver biopsies suggests that inflammatory activity is usually mild in children with chronic HCV infection.[13,14] There are however, reported cases of bridging fibrosis, cirrhosis and hepatocellular carcinoma in the literature.[14–16] Although liver fibrosis in children can be stabilised or reversed with pegylated interferon and ribavirin antiviral therapy,[17,18] the best method for reducing the risk of disease progression from HCV is early identification and initiation of antiviral treatment. In Australia, treatment has been limited by incomplete identification of cases and, in the past, availability of therapy.[19] In the current era of oral pangenotypic treatment for HCV, with rates of cure greater than 90%, it is even more important to identify children at risk early and treat them if they do not clear the virus spontaneously.[20]

The incidence and risk factors for childhood HCV infection in Australia are poorly defined. Australian studies of paediatric HCV infection report a bleak picture including: variable antenatal screening in high-risk groups,[21] lack of parental understanding of HCV transmission and a reluctance to screen children,[22] and poor coordination and follow up of HCV infected children in some centres.[21] Increasing our understanding of risk factors and presentation in childhood HCV is important to improve outcomes and service delivery to infected children. Therefore the aim of our study was to use national active surveillance to determine the incidence of newly diagnosed HCV infection in children presenting to Australian paediatricians and to describe the risk factors, clinical presentation, investigation, management, and co-infection with hepatitis B virus (HBV) and human immunodeficiency (HIV) in these children.

Methods

Children were identified through the Australian Paediatric Surveillance System (APSU)[23] from 1st January 2003, to 31st December 2007. The APSU conducts active national surveillance of rare childhood conditions, through monthly reporting by paediatricians (>1300).

Eligible children were aged <15 years with a newly diagnosed HCV infection. A confirmed case of HCV infection was defined as: 1) at least one confirmed positive anti-HCV antibody test performed ≥ 18 months of age, or 2) a positive anti-HCV antibody test on a single occasion and a positive test for HCV RNA (PCR or RT-PCR) on a single occasion at any age >1 month of age, 3) or a positive HCV RNA test (PCR or RT-PCR) on two separate occasions.

Once an eligible child with a newly diagnosed HCV infection was notified, the reporting paediatrician completed a study questionnaire. Data collected included the child's age, country of birth, date of diagnosis, sex, maternal country of birth, known child and maternal risk factors for HCV (e.g. perinatal, recipient of blood/blood product exposure or organ transplant, and lifestyle exposures), co-infections (human immunodeficiency virus (HIV), hepatitis B (HBV)), maternal HCV history, clinical symptoms, diagnosis, liver function test results, and treatment.

Ethical approval for this study was obtained from University of New South Wales (HREC-02376). The protocol and questionnaire are available from www.apsu.org.au.

Statistical analysis

Comparisons of categorical data were undertaken using χ^2 test or Fisher's exact test for small cells, or one sample binomial t-test, where appropriate.

To estimate the minimum population incidence of HCV for children aged between 0 and 15 years, we used the 30 June 2001 age standardised data cube as recommended by Australian Bureau of Statistics and Australian Institute of Health and Welfare.[24] We summed the data for the population age categories to get a total population and then calculated the incidence rate per 100 000 with 95% confidence intervals (CI) as per standard calculations. Age is presented as decimal age. We compared proportions of maternal country of birth, and mode of birth to those reported in Australia's Mothers and Babies to the mid-year of the data collection period (2005) using z-tests.[25] We tabulated our incident cases by year and age categories with HCV cases (both 'newly acquired' and 'unspecified') reported to the National Notifiable Disease Surveillance System (NNDSS).[26]

Presentation of cells with small numbers and identifiable characteristics have been limited.[27] Statistical analysis was done using SPSS version 22.0 (SPSS Inc. Released 2013. PASW Statistics for Windows, Version 22.0, Chicago: SPSS Inc.).

Results

There were 92 notifications over the five year study period, and detailed questionnaires were provided for 80 (87% response), of which 45 were confirmed cases of childhood HCV infection. The remaining notifications were either reporting errors ($n = 26$), or duplicate notifications ($n = 9$). Of the reporting errors, age was a common error with 7 children aged ≥15 years. Notifications were evenly distributed over the study period ($P = 0.50$). The reported incidence was 0.21 (95% CI 0.15 to 0.27) per 100 000 children <15 years. There were approximately six fold ($n = 265$) more HCV notifications reported to the NNDSS for the same age range and time period (Table 1).

Demographic and birth characteristics of HCV infected children

The median age at diagnosis of HCV infected children was 2.95 years (range 1.1 months to 14.87 years) (Fig. 1). There were no sex differences ($\chi^2 = 0.22$, df = 1, $P = 0.64$), and the majority of children was Australian born (Table 1). Indigenous status was not reported. Most children were born by normal vaginal delivery, and route of delivery was not statistically different from national reported birth data (29.4% vs. 22%, z-test 1.9, $P = 0.64$). Mothers of HCV infected children were predominantly Australian born (72%), and the proportion was not statistically different to Australian birth record data (76.8%, z-test 1.6, $P = 0.10$). There was no identified pattern to the country /region of maternal origin (e.g. Asia or European) (Table 2).

Table 1 Notification of childhood cases of HCV by year and age on the NNDSS† and the APSU‡, 2003–2007

	2003		2004		2005		2006		2007	
Age	NNDSS	APSU	NNDSS	APSU	NNDSS	APSU	NNDSS	APSU	NNDSS	APSU
0–4	26	5	40	8	19	5	22	4	24	2
5–9	6	3	10	1	10	1	9	0	10	4
10–14	12	3	10	3	12	2	62	4	22	0
Total	44	11	60	12	41	8	93	8	56	6

†NNDSS, National Notifiable Disease Surveillance System, newly acquired cases, and unspecified cases combined.[26]
‡APSU, Australian Paediatric Surveillance Unit, incident cases.

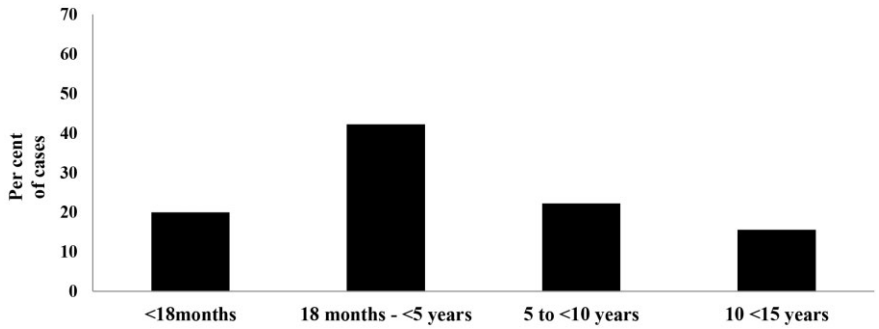

Fig. 1 Age distribution of incident cases of HCV in childhood (<15 years) reported to the APSU, 2003–2008 Australia.

Indications for HCV investigation, child and maternal HCV risk factors and diagnostic tests

Information on the 'reason for investigation' of the child was reported for 38/45 cases. The most frequent reason stated for HCV investigation was known maternal HCV infection. For six children (aged 1.4 to 11.6 years), investigation for HCV was prompted by identification of abnormal liver function during investigations for another illness (Table 3).

HCV risk factors were reported for all children. The most frequent risk factor was maternal HCV infection but three children (all aged >14 years), were exposed through their own IV drug use. Other risk factors included receipt of immunisation or injections in countries outside Australia (Table 3).

Maternal risk factors were well reported (Table 3). The majority of mothers of HCV infected children were reported to have a history of IV drug use. One mother reported blood/blood product exposure, three women reported possible exposure through other health care (e.g. childhood surgery). Other risk factors included other drug use,[3] tattooing and/or body piercing,[9] or needlestick injury.[2] No mothers were reported to be health care workers and or to have been incarcerated. Ten women reported multiple risk factors for HCV including combinations of IV drug use and tattoo/body piercing, blood/blood product and other needlestick injury (Table 3). Only one of the overseas born mothers was reported to be an IV drug user.

Maternal HCV and other blood borne virus results

Positive maternal HCV serostatus was reported for 40 children. Of the four mothers with a known date of HCV diagnosis, two

Table 2 Demographic and birth characteristics of HCV infected children aged <15 years in Australia, 2003–2007

Variable	N = 45
Sex	
Male	19
Female	22
Not reported	4
Median age at notification (years) (min, max)	3.0 (1.1 months, 14.9 yrs)
Child country of birth	
Australia	39
Other†	5
Not reported	1
Maternal country of birth	
Australia	32
Other‡	6
Not reported	7
Mode of Birth	
Vaginal	20
Assisted vaginal	2
Caesarean section	10
Not reported	13
Breast feeding	
Any	14
Not reported	31

†France, Japan, Kyrgyzstan, Pakistan, USSR.
‡France, Japan, Kyrgyzstan, New Zealand, Pakistan, USSR, Vietnam.

Table 3 Indication for HCV testing, child and maternal HCV risk factors

Variable	N = 45
Reason for testing child for HCV	
Known maternal HCV infection	29
Other carer infected	2
Routine investigation for other illness	6
Not stated	8
Known child HCV risk factors†	
Mother HCV positive	39
Infected family member	13
Child transfusion recipient	2
Child IV drug	2
Other immunisation/IM injections	2
Known maternal HCV risk factors†	
IV Drug use	31
Tattoo/body piercing	9
Other health care	3
Other drug use	3
Needlestick injury	2
Blood/blood product recipient	1
Not known/not reported	9
Maternal co-infection	
HIV (*n* = 31 tested)	2
HBV (*n* = 26 tested)	2

†Multiple risk factors.

were diagnosed during antenatal care. Maternal HCV RNA results were reported for 23/46, of which 20 were positive. Results of maternal testing for these other blood borne viruses were not available in all women. Of those tested, two HCV infected mothers were co-infected with HIV alone, and two others with HBV alone (Table 3).

Clinical features and laboratory testing

Almost all children were asymptomatic (40/45) at the time of HCV diagnosis with no reports of jaundice, or signs of liver failure. Two children had hepatomegaly, and one had bruising.

Eight children were aged <18 months at the time of their HCV diagnosis. All were HCV antibody positive and RNA positive. Almost all children were tested for HCV antibody (41/45), and all tested were seropositive. A repeat HCV antibody test was reported for 21 children (aged 1 month to 15 years) of whom 18 were positive, one child aged <18 months was indeterminate on repeat test but the RNA test was positive.

Of the 41 seropositive children, 39 were tested and positive for HCV RNA. Of these, genotype was reported for nine children, six children were infected with HCV genotype 1 (1 = 1, 3 = 1a, 1 = 1b, 1 = 1a/b), one with genotype 2, and another two with genotype 3a.

Liver function tests were reported for 46/48 children. LFT abnormalities at any time were reported for 29/46; the highest reported ALT was 379 and the highest AST level was 232. Two children had liver biopsies both of which were abnormal: one showed mild fibrosis and moderate inflammation and the other mild steatosis, minimal necroinflammatory activity, and no fibrosis. No children were reported to be co-infected with HIV, although the status of 13 was 'unknown'. Only one child was reported to be co-infected with HBV, the status of another nine was 'unknown'.

Therapy

Information on therapy for HCV was available for 41/45: no child had been treated with antiviral therapy at the time of the notification. Open field comments regarding ongoing clinical care suggested that there was frequent non-attendance at clinic appointments despite attempts by clinic staff to engage families.

Discussion

This five year national surveillance for newly diagnosed childhood cases of HCV suggests a minimum incidence of <1 per 100 000 children aged <15 years in Australia. The median age at diagnosis was just before the third birthday, only a small number of children being identified under 18 months). This is despite the fact that most of these children are from high risk groups with mothers who were HCV positive and using IV drugs.

We identified 45 newly diagnosed cases of childhood HCV infection over the study period through the APSU mechanism and obtained detailed epidemiological data not available through passive reporting systems. Our data are likely to be an under-estimate of the true incidence. Comparison with passive laboratory notifications of newly acquired and unspecified HCV infections made through the NNDSS showed that there were approximately six-fold more cases identified through the latter system for the same time period. The reasons for the difference are likely to be differences between the two mechanisms: the APSU relies on active reporting of HCV cases referred to specialist paediatricians in response to a monthly prompt, but this relies upon voluntary reporting and paediatricians are unlikely to see all cases. The NNDSS mechanism is mandatory through pathology providers, so ascertainment may be higher but it does not obtain detailed epidemiological and clinical information. Similarly, a discrepancy was noted when incident cases referred to a liver clinic at a NSW children's hospital were compared with state-based public health notifications for the same period.[28] These examples provide evidence of the gap between identification of HCV infection in children and referral to specialty child services.

HCV incidence estimates obtained through modelling[29] suggest that there are between 125 – 250 children born each year in Australia who are infected with HCV.[30] This suggests that mandatory laboratory notification systems also underestimate disease burden. Reasons for this include under detection of HCV infected mothers during the antenatal period and therefore suboptimal HCV screening of all HCV exposed infants and children. Antenatal screening practices varied in widely Australia during the period of surveillance.[21,31] The most recent statement from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommends all pregnant women should be screened for antibody to HCV[32] and differs to the current Australian national HCV testing policy.[33] Antenatal screening does

not confer benefit on vertical transmission rates but does improve outcomes for infected children.[28,31,34] Previous Australian data highlighted that knowledge of HCV vertical transmission and uptake of screening remains low in high risk populations, and suggests that novel educational strategies are needed to improve health outcomes in HCV exposed infants and children.[22,31] The antenatal period is an excellent opportunity for HCV screening, with 99.9% of women in Australia having at least one antenatal visit, and almost 95% having greater than five.[35] Data on screening for HCV infected mothers and children for HIV and HBV co-infection in our study were often not available and suggest that there may be missed opportunities for screening of other blood-borne viruses too. Antenatal screening will provide opportunities for improved care of HCV infected women and their infected offspring, including specialist paediatric care and vaccination for hepatitis A (after 2 years of age).[30]

However, even if a women is identified as HCV seropositive through antenatal screening, previous research suggests less than 20% of infected mothers have their children tested for HCV as they assume the children are not HCV positive.[22] Failure to test means children miss early opportunities for diagnosis and monitoring and mothers and carers miss opportunities for education and counselling and there is a future risk of infection for subsequent pregnancies.[22] Further, there are considerable public health costs of under-ascertainment. A US study in 2011 estimated that chronic HCV infection costs approximately US$65 000 per person, and these costs are significantly increased in children with a longer period of disease infection.[36] Early detection and improved ascertainment will both improve clinical outcomes but also reduce health costs.

Injecting drug use was the most frequent maternal risk factor for HCV infection, and in older children was also an identified risk factor for infection. This knowledge offers an important target group for prevention. Globally, the HCV disease burden due to injecting drug use has recently been estimated to account for over 500 000 DALYs (disease adjusted life years).[37]

Data on long term outcomes were not available from this study, due to low attendance by families to health providers and loss to follow-up by reporting clinicians. Serial data were also not routinely collected so we were unable to describe the proportion of HCV infected children who subsequently cleared their infection. However Australian data suggests that the natural history of paediatric disease involves a long asymptomatic period, and that treatment should be considered early especially in children co-infected with HIV.[19,38]

No child in this study was receiving therapy at the time of notification. Treatment options for HCV infection in children were limited during the surveillance period.[13] However, since that time curative therapy has emerged and therefore timely identification of childhood HCV is an imperative. Child health providers should therefore promptly refer infants and children with newly diagnosed HCV infection to a paediatric specialist with expertise in childhood HCV infection (usually a paediatric hepatologist). Specialist evaluation will include determination of HCV genotype and viral load, consideration of antiviral therapy and long term follow up for complications of HCV (liver disease, hepatocellular carcinoma), and advice regarding other hepatoprotective strategies (e.g. Hepatitis A vaccination). The decision to commence antiviral depends on many factors including the child's age (most wait til three years of age to start), HCV genotype, progression of liver disease, comorbidities, and social circumstances.

Strengths of the study include the quality and detail of data collected from paediatricians across the nation using the APSU mechanism, which has very high monthly reporting rates.[23] Limitations of this study include the small sample size, which we infer is mostly due to the lack of uniform guidelines for antenatal HCV testing and coordinated services for follow-up and investigations of exposed or high risk children. Lack of complete information on families and poor follow-up are a function of conducting research in people, including illicit drug users, who have limited engagement with the health system.[21] Improved coordination of HCV services between antenatal and child health providers and increased awareness of new, potential curative therapies by families and carers of HCV exposed infants and children could increase screening rates and follow up of these children nationally.

To our knowledge this is the first national Australian study since the introduction of blood and blood product screening to estimate the incidence and document known risk factors for HCV infection in children. It is important that clinicians opportunistically investigate HCV status in high risk infants and children when they intersect with the health care system. Key opportunities include antenatal and perinatal visits and other early childhood visits for vaccination. Testing for HCV antibody and liver function or HCV-RNA at 18 months of age or older will identify infected children and informed consent for testing should be sought.[30] Given the frequent loss to follow-up of these children due to family dysfunction, HCV-RNA testing in young infants from three months of age is also appropriate for identifying infection.[22,30,39] HCV testing in younger infants is insensitive (i.e. the test can yield false negative results). Although HCV RNA testing is recognised as the best diagnostic test for HCV in infants < 18 months of age, to date Medicare rebate is not available for this indication. With the anticipated increase in vertical transmission of HCV, improved education for primary care and other antenatal care providers regarding screening of infectious diseases in pregnancy is essential for improving outcomes.[40,41]

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