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ORIGINAL ARTICLĒLIVER, PANCREAS, AND BILIARY TRACT

Epidemiologic features of 348 children with hepatitis C virus infection over a 30-year period: a nationwide survey in Japan

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Abstract

Background Although the epidemiology of hepatitis C virus (HCV) infection among children may be rapidly changing, few reports have characterized large nationwide cohorts of children with HCV infection. We, therefore, sought to clarify the epidemiology and natural history of HCV infection in Japanese children born over the last three decades.

Methods Sixty-five pediatric centers retrospectively and prospectively recruited consecutive, otherwise-healthy HCV-infected children born during 1986 to 2015.

Results Entry criteria were met by 348 children. Age at initial diagnosis of infection has decreased significantly in recent years. Cirrhosis and hepatocellular carcinoma were not identified. Prevalence of spontaneous clearance and of interferon treatment with/without ribavirin were 9 and 54%, respectively. Maternal transmission has increased significantly, representing over 99% of cases in the last decade. No transfusion-related cases have been seen after 1994. HCV genotype 2 has increased to become the most prevalent in Japanese children. Histopathology examination of liver specimens showed no or mild fibrosis in most children with chronic hepatitis C; none showed cirrhosis.

Conclusions This largest nationwide cohort study of Asian children with HCV infection spanned the last three decades. None of these Japanese children developed cirrhosis or hepatocellular carcinoma. Maternal transmission increased to account for 99% of cases during the last decade. Genotype 2 now is most prevalent in these children. Histopathologically, most children with chronic hepatitis C showed mild fibrosis or none.

Keywords Natural history · Maternal transmission · Genotype · Liver histopathology · Cirrhosis

Abbreviations

HCV	Hepatitis C virus
anti-HCV	Anti-HCV antibody
SVR	Sustained virologic response
IFN	Interferon
RBV	Ribavirin
CHC	Chronic hepatitis C
SD	Standard deviation
DAAs	Direct-acting antiviral agents

Introduction

Hepatitis C virus (HCV) infection is a major cause of liver disease. Recent estimates showed an increase in its worldwide prevalence over the last decade to 2.8%, amounting to

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over 185 million infections [1–3]. In Japan, estimated prevalence of HCV infection in adults has been 0.8 to 1.2% [4]. Prevalence is lower in children, estimated at 0.012% at ages 5–9 years, 0.010% at 10–14 years, and 0.022% at 15–19 years [5]. The low prevalence of HCV infection in children reflects disappearance of transmission by blood transfusions and other medical procedures, and also reduced mother-to-child (i.e., vertical or perinatal) transmission, even though this form of transmission currently is responsible for most new infections in developed countries [6–9]. Among HCV genotypes, genotype 1 is most prevalent worldwide (49.1%), followed by genotypes 3 (17.9%), 4 (16.8%), and 2 (11.0%). Genotypes 5 and 6 are responsible for the remaining infections, representing less than 5% [3]. In Japanese adults, relative prevalence of genotype 1 has declined while that of genotype 2 has increased; nonetheless, genotype 1 (65%) remains more prevalent than genotype 2 (34%) [4, 10]. Taken together, these data raise the question of possible rapid changes in the epidemiology of HCV infection among Japanese children, but few large nationwide cohort studies of children with HCV infection have been undertaken, particularly in the last decade [9, 11, 12]. To evaluate the extent of these changes, which could alter the future burden of HCV infection, we investigated epidemiologic features of a large nationwide cohort of children with HCV infection in Japan. Specifically, we aimed to clarify the epidemiology and natural history of HCV infection in Japanese children who were born over the last three decades.

Methods

Study design

This study was designed and conducted within the framework of the "Observatory for HCV Infection and Hepatitis C in Japanese Children," established in 2011 by the Hepatology Group of the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition (JSPGHAN) with the aim of taking a census of children with HCV infection and investigating clinical aspects and outcomes of liver disease in this inadequately studied population. Sixty-five pediatric centers in Japan were involved in this survey. Over approximately 4 years, each of these centers retrospectively and prospectively collected all anti-HCV antibody (anti-HCV)-positive cases in children born from 1986 to 2015. Baseline and follow-up clinical information were obtained from patient records. Patient characteristics, clinical diagnosis at last visit, treatment, type of exposure, HCV genotype, and histopathologic features of liver biopsy specimens were determined. Features of the patients were evaluated in three groups defined by birth year: 1986–1995, 1996–2005, and 2006–2015. Some of these patients have been involved in previous studies [12–14]. The study protocol complied with the ethical guidelines of the Declaration of Helsinki of 1975 (2004 revision) and was approved by the ethics committee of Osaka General Medical Center and other participating centers.

Patients

Inclusion criteria were age between 0 and 16 years at initial diagnosis, birth between 1986 and 2015, HCV RNA positivity in at least one serum sample, follow-up for at least 1 year after the infection was diagnosed at the observatory center, and absence of coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV).

Clinical definitions were as follows. Spontaneous sustained clearance (in untreated HCV RNA-positive patients) signified disappearance of HCV RNA from at least two consecutive serum samples. Carriers were HCV RNA-positive patients with persistently normal serum alanine aminotransferase (ALT) concentrations. Chronic hepatitis was diagnosed in HCV RNA-positive patients with persistently increased ALT for more than 6 months or a liver biopsy specimen showing chronic hepatitis. Sustained virologic response (SVR) indicated HCV RNA negativity for 24 weeks following conclusion of interferon (IFN) treatment with/without ribavirin (RBV). Evidence of cirrhosis was diagnosed by liver biopsy or by clinical findings (jaundice, fatigue and/or edema), blood tests (hyperbilirubinemia, thrombocytopenia, hypoalbuminemia, and/or coagulopathy), and/or abdominal imaging including the liver using ultrasonography, computed tomography and/or magnetic resonance imaging (ascites, nodularity of the liver, and/or atrophy of the liver).

Type of HCV exposure

Putative types of HCV exposure were evaluated by concordant results of HCV genotype between mother and child and by ascertaining family history and past surgical and transfusion histories.

HCV RNA and genotype

HCV RNA was quantified in fresh or well-preserved stored sera by commercial quantitative assays such as real-time PCR (COBAS Ampliprep/COBAS TaqMan HCV test, Roche) in 90% of subjects, amplicor HCV monitor (COBAS Amplicor HCV Monitor test v 2.0, Roche) in 8% and branched DNA probe (Quantiplex HCV RNA 2.0, Bayer) in 2%. Genotype was assessed by genotyping assay using reverse transcription PCR of the core region with the genotype-specific primers in 82% of subjects and by serotyping assay in 18% according to the international classification [15, 16].

Histopathology

Histopathology of the liver was evaluated using initial liver biopsy specimens obtained from children with chronic hepatitis C (CHC) before they had received any IFN treatment with/without RBV. Liver biopsy specimens were assessed pathologically based on the New Inuyama Classification of chronic hepatitis [17], in which chronic hepatic disease is characterized according to degree of fibrosis (F) as follows: F0 (no fibrosis, equivalent to Ishak stage 0), F1 (fibrosis evident as portal expansion, equivalent to Ishak stage 1–2), F2 (bridging fibrosis, equivalent to Ishak stage 3), F3 (bridging fibrosis with lobular distortion, equivalent to Ishak stage 4), or F4 (cirrhosis, equivalent to Ishak stage 5–6) [17, 18]. Additionally, the classification assesses chronic hepatic disease activity (A) based on degree of lymphocytic infiltration and necrosis of hepatocytes as follows: A0 (no necro-inflammatory reaction), A1 (mild necro-inflammatory reaction), A2 (moderate necro-inflammatory reaction), and A3 (severe necro-inflammatory reaction) [17].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Chi squared, Fisher's exact, ANOVA, Tukey–Kramer, and Pearson correlation tests were used as appropriate. All statistical analysis was performed using GraphPad Prism version 6.05 software (GraphPad Software, San Diego, CA, USA). Tests were two-sided. *P* values below 0.05 were considered to indicate statistical significance.

Results

During this survey, participating centers enrolled 441 consecutive anti-HCV-positive children, among whom 348 children met entry criteria. Based on birth year, they were assigned to one of three groups: group 1, including 49 children born between 1986 and 1995; group 2, including 175 born between 1996 and 2005; or group 3, including 124 born between 2006 and 2015 (Fig. 1). Ninety-three children were excluded from this study for the reasons such as unknown RNA positivity, follow-up for less than 1 year, or presence of coinfection with HIV or HBV.

Patient features

Table 1 summarizes distribution of gender, age at initial diagnosis of infection, age at last clinical visit, clinical diagnosis at last visit, and treatment in the three groups.

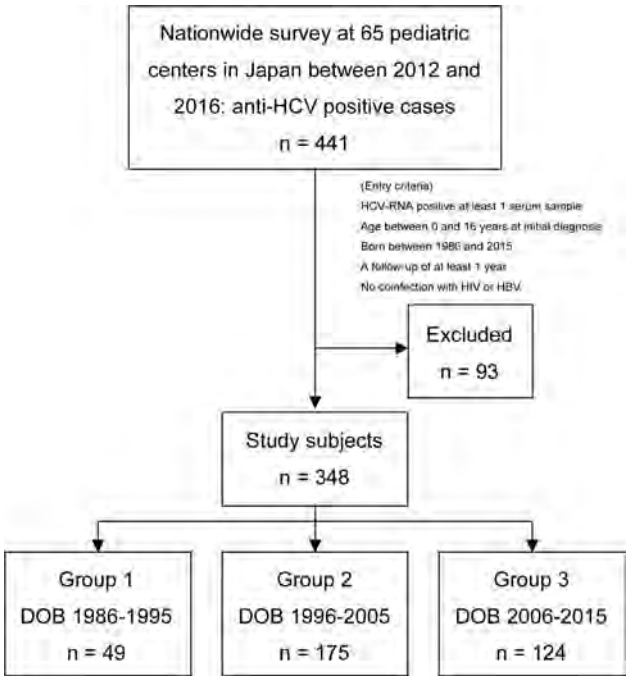

Fig. 1 Flow chart of this study. This chart summarizes entry criteria and distribution of patients into groups according to birth year. *HCV* hepatitis C virus, *anti-HCV* anti-HCV antibody, *n* number of patients, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus, *DOB* date of birth

Girls accounted for 56% of patients. Age at initial diagnosis of infection had decreased significantly in recent years ($P < 0.0001$). As for clinical diagnosis at last visit, frequencies of spontaneous clearance, carrier state, chronic hepatitis, and SVR were 9, 34, 4, and 40%, respectively. Carriers had increased significantly in recent years ($P < 0.0001$), and SVR had decreased significantly ($P < 0.0001$). Cirrhosis and hepatocellular carcinoma were not identified. The overall fraction of patients who received IFN treatment with/without RBV in recent years was 54%, having decreased significantly ($P < 0.0001$).

Type of HCV exposure

Table 2 characterizes the 348 children based on putative type of exposure to HCV in the three groups. Maternal transmission, the most frequent source of infection in all groups, accounted for 90% of infections overall, with a significant increase in recent years ($P < 0.0001$), increasing to over 99% in the last decade. Transfusion was the second most frequent source of infection in the earliest decade, while no transfusion-related cases have been seen since 1994. Only 17 cases (5%) were ascribed to other putative sources of infection, horizontal transmission or unknown source.

Table 1 Demographic and clinical features of the 348 children enrolled in the study

	Total ($n = 348$)	Group 1 1986–1995 ($n = 49$)	Group 2 1996–2005 ($n = 175$)	Group 3 2006–2015 ($n = 124$)	P values[a]
Male, n (%)	154 (44)	21 (43)	79 (45)	54 (44)	0.9418
Age at diagnosis of infection, months[b,f]	37.7 ± 45.2	76.7 ± 59.6	43.0 ± 44.1	13.0 ± 16.0	<0.0001
Age at last visit, months[b,f]	130.7 ± 70.2	240.6 ± 49.6	148.9 ± 38.0	61.7 ± 28.8	<0.0001
Clinical diagnosis at last visit, n (%)					
Spontaneous clearance	30 (9)	1 (2)	13 (8)	16 (13)	0.0525
Carrier[c]	120 (34)	9 (19)	45 (26)	66 (53)	<0.0001
Chronic hepatitis	15 (4)	1 (2)	6 (3)	8 (6)	0.3134
Sustained virologic response[d]	139 (40)	33 (67)	88 (50)	18 (15)	<0.0001
During treatment	16 (5)	1 (2)	9 (5)	6 (5)	0.6488
Unknown	28 (8)	4 (8)	14 (8)	10 (8)	0.9993
Cirrhosis/HCC	0/0				
Treatment (IFN with/without RBV), n (%)[e]	188 (54)	37 (76)	118 (67)	33 (27)	<0.0001

n number of patients, *HCC* hepatocellular carcinoma, *IFN* interferon, *RBV* ribavirin

[a] Comparison among the 3 groups by Chi squared or ANOVA tests

[b] $P < 0.0001$, Group 1 vs. Group 2, Group 1 vs. Group 3, and Group 2 vs. Group 3 by Tukey–Kramer test

[c] $P < 0.0001$, Group 1 vs. Group 3 and Group 2 vs. Group 3 by Fisher's exact test

[d] $P = 0.0364$, Group 1 vs. Group 2; $P < 0.0001$, Group 1 vs. Group 3 and Group 2 vs. Group 3 by Fisher's exact test

[e] $P < 0.0001$, Group 1 vs. Group 3 and Group 2 vs. Group 3 by Fisher's exact test

[f] Mean ± standard deviation

Table 2 Putative types of exposure to HCV infection in 348 children

	Total ($n = 348$)	Group 1 1986–1995 ($n = 49$)	Group 2 1996–2005 ($n = 175$)	Group 3 2006–2015 ($n = 124$)	P values[a]
Maternal, n (%)[b]	314 (90)	30 (61)	161 (92)	123 (99)	<0.0001
Horizontal, n (%)	2 (1)	0	2 (1)	0	0.3700
Transfusion, n (%)[c]	17 (5)	17 (35)	0	0	<0.0001
Unknown, n (%)[d]	15 (4)	2 (4)	12 (7)	1 (1)	0.0398

n number of patients

[a] Comparison among the three groups by Chi squared test

[b] $P < 0.0001$, Group 1 vs. Group 2 and Group 1 vs. Group 3; $P = 0.0054$, Group 2 vs. Group 3 by Fisher's exact test

[c] $P < 0.0001$, Group 1 vs. Group 2 and Group 1 vs. Group 3 by Fisher's exact test

[d] $P = 0.0176$, Group 2 vs. Group 3 by Fisher's exact test

HCV genotype

Table 3 characterizes 298 of the children based on the HCV genotypes in the three groups. Overall relative prevalences of genotypes 1, 2, and 3 were 42, 57, and 1%, respectively. Genotype 1 has decreased significantly in recent years ($P = 0.0427$), while genotype 2 has increased ($P = 0.0775$).

Histopathology

Table 4 summarizes the demographic and clinical features of 147 children with CHC who underwent liver biopsy between 1995 and 2015, while Table 5 presents the histopathologic features of the liver according to the New Inuyama Classification [17]. Mean age at biopsy was 8.9 ± 4.0 years. The distribution of degree of necro-

Table 3 HCV genotype in 298 children

	Total ($n = 298$)	Group 1 1986–1995 ($n = 44$)	Group 2 1996–2005 ($n = 158$)	Group 3 2006–2015 ($n = 96$)	P values[a]
Genotype 1, n (%)[b]	126 (42)	25 (57)	68 (43)	33 (34)	0.0427
Genotype 2, n (%)	169 (57)	19 (43)	89 (56)	61 (64)	0.0775
Genotype 3, n (%)	3 (1)	0	1 (1)	2 (2)	0.4095

n number of patients

[a] Comparison among the three groups by Chi squared test

[b] $P = 0.0162$, Group 1 vs. Group 3 by Fisher's exact test

Table 4 Demographic and clinical features of 147 children with chronic hepatitis C who underwent liver biopsy between 1995 and 2015

Male, n (%)	70 (48)
Age at biopsy, years[a]	8.9 ± 4.0
Duration of infection, years[a] (maternal transmission, $n = 127$)	8.4 ± 3.6
Type of exposure, n (%)	
Maternal	127 (86)
Transfusion	10 (7)
Horizontal or unknown	10 (7)
HCV genotype ($n = 131$), n (%)	
Genotype 1	63 (48)
Genotype 2	66 (50)
Genotype 3	2 (2)

n number of patients

[a] Mean ± standard deviation

Table 5 Histopathologic features of liver biopsy specimens from 147 children with chronic hepatitis C

N (%)	A0 (5)	A1 (74)	A2 (20)	A3 (1)
F0 (33)	6	34	8	0
F1 (58)	2	70	12	1
F2 (9)	0	5	9	0

n number of patients, *A0* no necro-inflammatory reaction, *A1* mild necro-inflammatory reaction, *A2* moderate necro-inflammatory reaction, *A3* severe necro-inflammatory reaction, *F0* no fibrosis, *F1* fibrosis with portal expansion, *F2* bridging fibrosis

inflammatory activity (A0, A1, A2, and A3) was 5, 74, 20, and 1%, respectively. The distribution of degree of fibrosis (F0, F1, and F2) was 33, 58, and 9%, respectively. F3 and F4 were not seen. No significant correlation was found between degree of fibrosis and age at biopsy or duration of infection (Supplementary Figs. 1 and 2). Degree of fibrosis was not related to gender, type of exposure, or genotype (Supplementary Tables 1 to 3).

Discussion

Few reports describing large nationwide cohorts of children with HCV infection are available, although recent reports concerning adults indicate that the epidemiology of HCV infection is changing dramatically worldwide [1–3, 9, 11, 12]. We investigated the epidemiologic features of Japanese children with HCV infection to clarify natural history and trends over the last three decades. Previous large nationwide cohort studies of children with HCV infection describe epidemiologic features observed about two decades before 2006 [9, 11, 12]. Our investigation represents the largest nationwide cohort study of Asian children with HCV infection over a 30-year period, including children born during the most recent decade, 2006–2015. Additionally, we included a large pediatric-age survey of HCV histopathologic features, characterizing 147 children with CHC.

Since HCV was discovered in 1989 [19, 20], the Japanese Red Cross has screened blood donors for anti-HCV with a first-generation assay beginning in 1989, or, since 1992, a second-generation assay [21]. The present study shows that because of screening, transfusion transmission has decreased dramatically, and transfusion-related cases have disappeared after 1994. Three patients had putative transfusion transmission between 1992 and 1994, most likely because risk of fibrinogen-transmitted HCV infection was yet to be eliminated in Japan during that period [22]. At present maternal transmission accounts for 99% of cases, representing nearly the sole route for pediatric-age HCV infection. Comparing group 2 (born from 1996 to 2005) with group 3 (2006–2015), ages at time of diagnosis steadily decreased. We believe that this change reflects heightened awareness of maternal transmission of HCV among Japanese obstetricians and pediatricians; nearly all pregnant women in Japan now are screened for anti-HCV.

Girls were somewhat more numerous than boys among our subjects (56%) and spontaneous clearance occurred in 9% of patients, in essential agreement with previous reports [9, 11, 23]. IFN treatment with/without RBV was given to 54% of patients. Suzuki et al. reported that pegylated IFN monotherapy and pegylated IFN combined with RBV both produced encouraging results against HCV infection and were well tolerated and reasonably safe in Japanese children and adolescents with CHC, including some enrolled in this study [13]. Interestingly, our survey identified no patients with cirrhosis. Bortolotti et al. reported that 2% of untreated children with HCV infection progressed to decompensated cirrhosis before 16 years of age [9]. We believe that none of our subjects showed cirrhosis because of racial differences, because roughly half of them received IFN therapy with/without RBV, or because of both factors.

Relative prevalence of HCV genotypes is changing worldwide. We found genotype 1 to be decreasing, as did a previous report of children with HCV infection in Italy [11]. Genotype 2 was increasing in our Japanese survey, in contrast with increases in genotypes 3 and 4 in Italy [11]. Notably, genotype 2 has become most prevalent (57%) in our pediatric survey, although a recent report concerning adults stated relative prevalences of genotypes 1 and 2 in Japan in 2011 as 65 and 34%, respectively [4]. Toyoda et al. reported that genotype 1 remains most common in adults born before 1970, although genotype 2 has become most prevalent in adults born in or after 1970. Additionally, about half of these younger infected adults had a history of intravenous drug use or tattooing (though not of blood transfusion) [24]. These results suggest that in Japan genotype 2 may have spread to young adults by drug use or tattooing and then to children by maternal transmission. Up-to-date knowledge of genotype frequencies in Japanese children will be important in considering future treatment options against HCV infection.

Histopathology examination of liver specimens from most children with CHC showed fibrosis to be absent or mild, with inflammation predominating. No cirrhosis was found. Table 6 summarizes the largest studies of liver biopsy findings in children with CHC from Europe, the US, and Japan [14, 25, 26]. Kage et al. reported that the liver showed absent or mild fibrosis in most untreated Japanese children with CHC, as well as absence of cirrhosis. However, transmission was different in that study, with transfusion accounting for 85% of cases [14]. In the present study, even though 86% of our patients who underwent liver biopsy had maternal transmission, we observed similar histopathologic features in untreated Japanese children with CHC, including absence of fibrosis in 33% of patients and absence of cirrhosis in all. In contrast, Guido et al. reported that liver histopathology showed cirrhosis in 1% of untreated children with CHC in Italy and Spain [25], while Goodman et al. found the frequency in the US to be 2% [26]. Additionally, fibrosis was absent in smaller percentages of specimens in these studies than ours (28% [25] and 14% [26] vs. 33%). Thus, Japanese children with CHC might have less risk of fibrosis and cirrhosis than chronically infected children in some Western countries. Some reports of adults with CHC have associated patient age and duration of infection with progression of fibrosis [27, 28]. In children with CHC, the present study and Goodman et al. showed no significant correlations of degree of fibrosis with age at biopsy or duration of infection, although Guido et al. found degree of fibrosis to correlate with both patient age and duration of infection [26, 29]. Additionally, Mohan et al. reported that sequential biopsy specimens demonstrated progression of fibrosis in children with CHC, aged 8.6 ± 4.1 years at the first biopsy and 14.5 ± 4.0 years at the second [30]. Accordingly, severity of fibrosis might be more closely related to age or duration of infection in adolescence and young adulthood than in childhood.

New direct-acting antiviral agents (DAAs) now are being developed at a remarkable pace. Combining DAAs targeting different stages in the viral proliferation cycle has proven highly effective, permitting development of IFN-free and largely RBV-free regimens that might be better tolerated. Such oral regimens now have shown cure rates exceeding 90% in most adult populations [31–33]. We soon should be able to treat children with HCV infection using the new DAAs [34]. The results of our study, particularly, those concerning genotype trends and histopathologic features, should be useful to pediatric hepatologists in Japan and elsewhere in considering treatment of children with HCV infection using the new DAAs.

HCV/HIV coinfection is highly prevalent in Asia [35]. Omata et al. reported that maternal transmission of HCV is affected significantly by coinfection with HIV, and safety and efficacy of recently developed DAAs and those under development in reducing maternal transmission, particularly in the presence of HIV coinfection, require further investigation [36]. In the present study, maternal transmission accounted for 99% in the last decade. We therefore should undertake curative treatment using new DAAs in young women with HCV/HIV coinfection before pregnancy in order to prevent maternal transmission.

An important limitation of this study is the retrospective nature of data from most patients, particularly those who are older. The group born from 1986 to 1995 is smaller than groups born from 1996 to 2005 or from 2006 to 2015, probably because of loss of patient record accessibility at pediatric centers following transition to adult health care. Clinical diagnosis at last visit and prevalence of treatment clearly differ between subjects born from 1986 to 2005 and

Table 6 Liver histologic findings in large studies of children with chronic hepatitis C

Author	Year	Country	Patients	Age at biopsy years, mean ± SD	Type of exposure, %		Fibrosis, %			
					Maternal	Transfusion	None	Mild	Bridging	Cirrhosis
Kage et al. [14]	1997	Japan	109	8.8 ± 4.2	11	85	96[a]		4	0
Guido et al. [25]	1998	Italy/ Spain	80	9.1 ± 4.8	60	24	28	55	16	1
Goodman et al. [26]	2008	US	121	9.8 ± 3.7	78	7	14	80	4	2
Present study	2017	Japan	147	8.9 ± 4.0	86	7	33	58	9	0

Fibrosis staging as follows: none, F0 or Ishak 0; mild, F1 or Ishak 1–2; bridging, F2-3 or Ishak 3–4; cirrhosis, F4 or Ishak 5–6

SD standard deviation

[a] Total of none and mild

those born from 2006 to 2015 because of differing length of the follow-up period.

In conclusion, we clarified the epidemiologic features and natural history of Japanese children with HCV infection over the last three decades. To our knowledge, this is the largest nationwide cohort study from Asia. Age at initial diagnosis of infection has decreased significantly. Cirrhosis and hepatocellular carcinoma did not develop. The proportion of maternal transmission significantly increased in the last decade to 99%. No transfusion-related cases have been seen since 1994. Genotype 2 has become most prevalent among Japanese children. Histopathologic examination of the liver showed fibrosis to be absent or mild in most children with CHC.

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Authors' contributions TM, TT, and HT contributed to the concept and design of the study. All authors contributed to analysis and interpretation of the data. TM and HT contributed to writing the manuscript. Thus, all authors contributed to the manuscript.

Compliance with ethical standards

Conflict of interest We have no conflict of interest.

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