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B 型肝炎疫苗接種後之兒童猛暴性肝炎現況:17 年之病例分析及全國性前瞻式研究(2/2)

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行政院國家科學委員會補助專題研究計畫√**成果報告**
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B 型肝炎疫苗接種後之兒童猛暴性肝炎現況:17 年之病例分析及全國性

前瞻式研究

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中文摘要:

為了解台灣全面施行 B 型肝炎所造成之兒童猛暴性肝炎之現況，我們執行此一全國性合作計畫，分析全台 1985 至 1999 年所有因猛暴性肝炎住院之 1 個月至 15 歲兒童(62 名男性及 33 名女性)；並分析他們的 B 型肝炎感染現狀(HBsAg and/or IgM-anti-HBc seropositive)，B 型肝炎感染占所有病患的 45% (43/95)，猛暴性肝炎的平均年發生率在 1 至 15 歲兒童為 0.053/100,000 、在一歲以下嬰兒為 1.29/100,000，猛暴性肝炎病患有 61%(58/95)為一歲一下之嬰兒。在 0-1 歲嬰兒中 B 型肝炎感染占猛暴性肝炎之 57%，而在 1 至 15 歲的兒童 B 型肝炎感染占 27%，比例嬰兒為較低(0.004)，以 B 型肝炎陽性的病例分析，一歲以上比一歲以下的發生率比(rate ratio)為 54.2，B 型肝炎陰性的病例，一歲以上比一歲以下的發生率比為(rate ratio)15.2。在母親帶原方面，母親表面抗原的陽性率在嬰兒並例為 97%，而這些病例中有 84%母親之 e 抗原均為陰性。所有 B 型肝炎病例中有 74%病例曾經打過 B 型肝炎疫苗、而 81%之一歲以下嬰兒曾經接種過 B 型肝炎疫苗。

在預後方面，所有病例的死亡率為 75%，死亡病例組年紀較高，總膽紅素較高，凝血時間較長，而 B 型肝炎帶原陽性率較低。B 型肝炎陽性組的死亡率有 65%，陰性組死亡率 83% (p=0.05)；陽性組及陰性組的危險因子不同；以 B 型肝炎陽性的病例來分析，死亡組有較高的凝血時間(p=0.036)；B 型肝炎陰性組的病例，年齡較大並有較高的總膽紅素值 ($P < 0.001$ and $P = 0.006$)，多因子分析顯示總膽紅素值是唯一的影響因子。分析年代的因素，發現 B 型肝炎陽性組的死亡率在三個年代區間(91, 67 and 38%, $P = 0.027$ in year 1985–1989, 1990–1994, 1995–1999) 有逐漸下降的趨勢，而 B 型肝炎陰性組的死亡率則在三個年代沒有明顯變化。

分析八位嬰兒期的猛暴性 B 型肝炎病例，病人的病毒濃度由 $1.8x\ 10^4$ to $1.9\ x\ 10^8$ copies/ml; 母親的病毒濃度為 $2.3\ x\ 10^3$ to $8.7\ x\ 10^7$ copies/ml，母親均為 e 抗原陰性之 B 型肝炎帶原者，病人的病毒量大多高於母親病毒量 (7/8)。病人的病毒量與預後沒有明顯相關，基因型除了一位病人之外全部是 B 型。

總結來說，在台灣實施 B 型肝炎疫苗接種 15 年內，B 型肝炎在一歲以上兒童已經很少造成猛暴性肝炎，但仍然是一歲以下嬰兒之猛暴性肝炎之重要原因，B 型肝炎造成的猛暴性肝炎容易在 e 抗原陰性的表面抗原帶原母親所生的嬰兒發生，這些嬰兒在目前我國的疫苗政策下並未接種 B 型肝炎免疫球蛋白。B 型肝炎陽性的猛暴性肝炎患者有較低的死亡率，而 B 型肝炎陽性與陰性者，其預後因子不同。嬰兒期得到猛暴性 B 型肝炎者通常有高病毒量，傳染來源最可能來自母親的陽性病毒血液。

關鍵詞：肝衰竭、B 型肝炎感染、兒童、疫苗接種、發生率

ABSTRACT

To investigate the role of hepatitis B virus (HBV) infection in pediatric fulminant hepatic failure (FHF) following the launch of universal HBV vaccination, we analyzed the data from patients with FHF collected from a nationwide collaborative study group. Children from one month to 15 years old who were diagnosed with FHF (62 males and 33 females) from 1985 to 1999 were included. HBV infection (HBsAg and/or IgM-anti-HBc seropositive) accounted for 45% (43/95) of all the cases of FHF. The average annual incidence of FHF in the years 1985 to 1999 was 0.053/100,000 in the one to 15-year-old population, and 1.29/100,000 in those below one year of age. Sixty-one percent (58/95) of all FHF cases were infants. The percentage of HBV infection was higher in infants (57%) than in one to 15-year-old children (27%) (p=0.004). The incidence rate ratio of those below one year of age to those aged one to 15 years was 54.2 for HBV-positive FHF and 15.2 for HBV-negative FHF. Maternal HBsAg was positive in 97% of the infants with HBV-positive FHF, and HBeAg was negative in 84%. Seventy-four percent of all HBV-positive FHF cases and 81% infantile HBV-positive cases were vaccinated.

The overall mortality rate was 75%. Patients in the mortality group were of an older age, had higher peak total bilirubin levels, a longer prothrombin time, and a lower percentage of HBV positivity ($P < 0.001$, $P = 0.003$, $P = 0.0027$ and $P = 0.042$, respectively). Mortality was 65% in the HBV positive ($n = 42$) and 83% in the HBV negative ($n = 52$) group ($P = 0.05$). In the HBV positive group, the prothrombin time was noted to be the single factor affecting outcome ($P = 0.036$). In the HBV negative group, older age and higher peak value of total serum bilirubin were suggestive of poor survival rate ($P < 0.001$ and $P = 0.006$, respectively). Multivariate analysis revealed that total bilirubin was the single factor affecting outcome in the HBV-negative group. The mortality rate of HBV positive children in three consecutive time periods without liver transplantation (1985–1989, 1990–1994, 1995–1999) decreased gradually (91, 67 and 38%, respectively, with $P = 0.027$). This change was not observed in HBV-negative cases.

The viral load of patients ranged from 1.8×10^4 to 1.9×10^8 copies/ml; the viral load of mothers ranged from 2.3×10^3 to 8.7×10^7 copies/ml. In all but one pair, patient's viral load was higher than mother's viral load. There was no correlation between patient's viral load and prognosis. The genotype was all B except on patient who was mixed B and C type.

In conclusion, within the first 15 years of universal vaccination, HBV rarely caused FHF in children above one year of age, but remained a significant cause of FHF in infants. HBV-positive FHF was prone to develop in infants born to HBeAg-negative, HBsAg-carrier mothers; these infants had not received HBIG according to our vaccination program. Hepatitis B virus positive FHF had a lower mortality rate than HBV negative FHF, with each group having different factors affecting mortality. Infants with fulminant hepatitis B had high viral load, likely to be transmitted from their HBsAg (+)/HBeAg(-) mothers with viremia.

關鍵詞(keywords): Hepatic Failure, Hepatitis B, Children, Vaccination, Incidence

目　錄

前言

Fulminant hepatic failure (FHF) is a clinical disease involving acute and severe impairment of liver function, encephalopathy and severe coagulopathy.[1,2] The cause of FHF has varied largely with location. The most frequent causes worldwide have been viral hepatitis A, B, and non-A non-B, accounting for 60% to 70% of all cases.[3-5] The prevalence of hepatitis B virus (HBV) infection in previous reports of FHF has ranged from 10% to 65%.[6-9] The mortality rate from FHF caused by HBV has been as high as 61% to 77%.[10-12]

Taiwan has been a highly endemic area of HBV infection; about 15% to 20% of the population have been chronic HBV carriers.13,14 HBV infections have caused 80% of the adulthood and nearly 100% of the childhood hepatocellular carcinoma (HCC).15-18 Before the implementation of hepatitis B vaccination, 65% of childhood fulminant hepatitis was caused by HBV infection. Of those, patients below one year of age accounted for 65% of the cases.10 Mother-to-infant transmission and blood transfusions were the major routes of infection. Most of the donors and mothers were HBsAg positive and anti-HBe positive.10,19-21

A universal vaccination program was launched in Taiwan in 1984.22,23 Before the vaccination program, the HBsAg positive rate in children under 12 years of age was 9.8%. Following the institution of the program, the HBsAg carrier rate in children decreased steadily: 4.8%, 1.3% and 0.7% in years 5, 10, 15, respectively.24,27 The annual rate of incidence in childhood HCC decreased from 0.52 to 0.13 per 100,000 children after the vaccination program.28 A trend showing a decrease in the number of acute hepatitis cases caused by HBV was also noted.29 Moreover, the mortality rate from hepatitis in infants declined.30

研究目的

In light of the high mortality rates produced in children with HBV-associated diseases, such as FHF and HCC, it is necessary to evaluate the progress of universal vaccination in the control of fulminant hepatitis. In this study, we recruited pediatric FHF patients in Taiwan during the first 15 years of the vaccination program in order to assess the current impact of HBV infection in these children. In addition, because FHF is a rare disease in children, the case series reported were limited and the case numbers were small. The analysis of mortality rate and prognostic factors according to disease etiologies was therefore difficult. Risk factors for mortality in patients with fulminant hepatitis B in children have not been reported. While orthotopic liver transplantation has become widely available, a detailed and updated outcome evaluation of pediatric FHF without liver transplantation is mandatory.

研究方法

Taiwan has a population of 22 million with approximately 330,000 births each year. During the period of this study, there were a total of nine tertiary referral centers in Taiwan, with a total bed count of 14,800. This study was conducted by the Childhood Fulminant Hepatic Failure Study Group, joined by the nine tertiary referral centers covering the north, central, and south parts of Taiwan. All hospitals included in this study were qualified through the availability of the facilities for pediatric intensive care and staffs specialized in pediatric gastroenterology.

Inclusion and exclusion criteria FHF cases. From January 1985 to December 1999, all the children aged 0 to 15 years admitted for FHF, regardless of the outcome, were included. This study was conducted retrospectively through review of hospital admission records. FHF was defined as the development of hepatic encephalopathy and coagulopathy within eight weeks of disease onset in patients without known preexisting liver diseases. Children younger than one month of age were not recruited in order to exclude cases caused by perinatal insults and inherited metabolic defects. Those with acute hepatic failure secondary to bacterial sepsis, drug intoxication, or total parenteral nutrition were also excluded. All patients included had hyperbilirubinemia with a direct bilirubin level above 2 mg/dl and coagulopathy with a prothrombin time two times the normal value.

A thorough search for known hepatitis viruses A to C, cytomegalovirus and Epstein-Barr viruses was conducted. HBV infection was defined by HBsAg and/or IgM-anti-HBc seropositivity.

Nationwide hepatitis B vaccination program. In Taiwan, 16% of pregnant mothers were HBsAg carriers.23,31 The Universal HBV vaccination program in Taiwan began on July 1, 1984. Hepatitis B immunoglobulin was administered to newborns of HBeAg-positive, HBsAg-carrier mothers within 24 hours after birth. The details of the vaccination program were described previously.23,28,32 The vaccine coverage rate was as high as 95%.26

Vaccination history and maternal HBV status. A vaccinated case was defined as the completion of three doses of the HBV vaccine in infants older than six months, or as having received appropriate doses by schedule in infants below six months of age. Maternal HBV status was recorded as HBsAg and HBeAg/Anti-HBe positivity.

Incidence of FHF in Taiwanese children. In Taiwan, all births, deaths and marriages must be registered with the government's household-registration offices. The year-end population statistics for children in this study were obtained from the annual reports on demographic statistics published by the Ministry of Interior. The incidence rates of FHF from 1985 to 1999 were thus derived from the numbers of the above-mentioned registered cases and the age-specific population data obtained from year-end population statstics.

Data from the Nationwide Mortality Registry. To compare nationwide pediatric mortality to hepatitis before and after the vaccination program, we used the National Mortality Registry System to study the mortality associated with all causes of hepatitis in children aged one to 15 years from 1980 to 1999. All death certificates, which must be registered in the household registration offices, were reviewed routinely and submitted to the national death certification system by the local health bureaus. All death certificates were reviewed and coded by medical registrars according to the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death in the central office of the national death certification system, Department of Health.

Statistics. Incidence rates and confidence intervals were calculated using the person-year approach. Actual person-year calculations were derived by multiplying the total number of children alive by the number of years each individual had survived during the pre-specified time span. Comparison of the frequencies of incidence that occurred during the pre-specified time period was made using the chi-square person-year approach.33 All comparisons were two sided

with p-values less than 0.05 considered statistically significant. The Stata package (Stata 7, College Station, TX) was used for all statistical analysis. The incidence rate ratio (IRR) was derived using Poisson regression to compare the difference between age cohorts.

Analysis for factors affecting mortality of fulminant hepatic failure in children. Patients were divided into survival ($n = 24$) and mortality ($n = 70$) groups. The age of onset, calendar year of admission, prothrombin time (PT) , levels of serum total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and HBV seropositivity were analyzed. Comparisons were also made between HBV positive ($n = 42$) and HBV negative ($n = 52$) patients. The calendar year of admission was divided into three periods: 1985–1989, 1990–1994, and 1995–1999.

Chi-squared tests and the Student's *t*-test were applied for statistical analysis. A *P*-value below 0.05 was considered to be significant. Statistical analysis was performed by using Statistical Products and Services Solutions, version 10.0 (SPSS Inc., Chicago, IL, USA). The variables, which were significant in the above analysis, were further investigated by using multivariate analysis. A cut-off value for significant continuous variables was calculated by the area under the receiver operator characteristics (ROC) curve. Multiple regression analysis was performed to adjust confounders simultaneously and to calculate multivariate-adjusted odds ratios for risk factors associated with mortality. The α level of model selection was set at 0.05 for entry and 0.1 for removal. A $P < 0.05$ was considered statistically significant.

Detecting Viral load and Genotyping. Serum samples from mother-infant pairs of cases with infantile fulminant hepatitis B were collected, to test the role of mother to infant transmission. A real-time PCR method detecting HBV viral load and genotyping simultaneously will be performed in mothers during pregnancy (Yeh SH, 2004). The reaction is based on LightCycler hybridization probes assay system. By PCR with primers highly conserved in all HBV genotypes, all viral genomes contained in the serum will be amplified equally. For detecting the target DNA, a proper pair of anchor and senor probes is used for detecting viral load. Within the sensor probe there exists signature single nucleotide polymorphisms (SNPs), which could effectively differentiate different HBV genotypes by showing different melting temperatures.

結果

Incidence. From 1985 to 1999, a total of 95 pediatric patients were diagnosed with FHF (M:F=62:33). HBV infection accounted for 45% (43/95) of all cases. Among the 52 HBV-negative cases, Wilson's disease was diagnosed in six cases, acute EBV infection in four, and infection-associated hemophagocytic syndrome in two. The remaining 40 cases were idiopathic. The case numbers and incidence of HBV-positive FHF and HBV-negative FHF are shown in Table 1. Overall, the average annual incidence of all FHF cases from 1985 to 1999 was 0.053 per 100,000 in the one to 15-year-old population and 1.29 per 100,000 in those below one year of age.

Age and gender differences. We analyzed the data on patients with FHF by two age groups: below one year and between one and 15 years old. Sixty-one percent (58/95) of patients with FHF were under one year of age, and 57% of them (33/58) were HBV-positive. The percentage of HBV infection in those aged between one and 15 years was 27% (10/37), which was lower than in those aged below one year (p=0.004). In all HBV positive cases, 77% (33/43) were infants. The incidence rate ratio of those below one year to those aged one to 15 years was 54.2 ($p<0.001$) in the HBV-positive FHF group and 15.2 ($p<0.0001$) in the HBV-negative FHF group (Table 1). The rates of HBV-positive FHF in the years 1985 to 1989, 1990 to 1994, and 1995 to 1999 were 42%, 70%, and 52% in infants (p=0.24); and 40%, 33%, and 13% in children one to 15 years (p=0.21), respectively.

We further compared the different incidences of age-stratified HBV-positive and HBV-negative FHF in different genders (Table 2). The male to female incidence ranged from 1.17 to 2.88. Male preponderance was statistically significant only in HBV-positive FHF that occurred below one year of age.

Maternal HBVstatus. In the 43 HBV-positive FHF patients, maternal HBsAg and HBeAg status was available in 35 and 26 cases, respectively. HBsAg was positive in 89% (31/35), and HBeAg was negative in 81% (21/26). Because the cases occurring in patients below one year of age were most likely to be infected through maternal-infant transmission, thus making maternal status a relevant factor in this group, we also calculated the rate of infants with mothers testing positive for HBsAg and HBeAg. Maternal HBsAg was positive in 97% (28/29) and HBeAg-negative in 84% (21/25) of the cases, respectively.

Vaccination history. In a total of 43 HBV-positive FHF patients, 39 HBV-positive FHF patients had available vaccination records and 29 (74%) of them were vaccinated. Seven of the ten unvaccinated children were born from 1985 to 1986, one in 1988, and the remaining two in 1990. After 1991, no case was unvaccinated. In a total of 33 infants below one year of age with HBV-positive FHF, 31 had a vaccination record. Twenty-five (81%) infants received one to three doses of the HBV vaccine, depending on the age of onset: three received one dose, 20 received two doses, and two completed 3 doses of vaccines. Totally 29 infants and children had acquired HBV-FHF despite compliance with the vaccination schedules.

Outcome. The total mortality rate of patients with FHF was 74%. The mortality rate was lower in HBV-positive patients than in HBV-negative patients (65% vs. 83%, p=0.05).

Nationwide Mortality Registry of Hepatitis. The mortality rate from hepatitis in infants before and after vaccination decreased from 5.36 to 1.71 per 100,000 in the population.30 The average annual mortality rate of children aged one to 15 years in the years 1980 to 1984 and 1985 to 1999 were 0.27 and 0.10, respectively. The incidence rate ratio from the period 1985 to 1999 to the period 1980 to 1984 was 0.37 ($p<0.01$).

Mortality analysis. Table 3 shows the clinical parameters of all FHF cases. Mortality cases were noted to have older age ($P < 0.001$), higher levels of total bilirubin ($P = 0.003$), longer PT levels ($P = 0.027$), and a lower rate of HBV seropositivity ($P = 0.042$). Patients in the mortality

group had higher peak levels of direct bilirubin, and lower peak levels of AST and ALT compared with those in the survival group, without statistical significance.

To investigate whether these prognostic factors differ in HBV-positive and -negative cases, we divided the patients into two groups for comparison (Table 2). The mortality rate in the HBV-positive group was 64% (27 of 42) compared to 83% (43 of 52) in the HBV-negative group. Older age and higher levels of total and direct bilirubin were noted in HBV-negative children than HBV-positive children.

Table 4 shows the mean values of the clinical variables between the mortality and survival groups of both HBV-positive and -negative FHF cases. The only significant difference between survival and mortality in HBV-positive cases was PT ($P = 0.036$). In HBV-negative cases, older age and higher levels of serum bilirubin affected the outcome ($P < 0.001$ and $P = 0.006$, respectively). There was no significant difference in PT levels. By using multivariate analysis in the HBV-negative group, peak bilirubin ($P = 0.012$), not age ($P = 0.237$), was found to be the single significant factor affecting outcome.

We further compared the mortality rates in different admission periods in the 15 years. Table 3 shows the changes of mortality rates over the three consecutive 5-year periods. The overall mortality rate of FHF in the consecutive three time periods (1985–1989, 1990–1994, 1995–1999) showed no statistical significance (78, 78, 70%, respectively). Moreover, HBV-positive cases decreased significantly in the consecutive three periods, from 91 to 67%, then to 38% ($P = 0.027$). This trend was not seen in HBV-negative FHF group (64, 73, and 73%, respectively, $P = 0.846$).

To test whether the decline in mortality of HBV-positive FHF was caused by changes in clinical severity over the years, we analyzed the biochemical parameters in these three time periods. No statistical differences in bilirubin and aminotransferase levels were found in HBV-positive FHF. The percentage of patients in the group of PT prolonged >50 s showed a trend of decline during these three time periods (97, 67, and 55%, respectively, $P = 0.084$).

Viral load in mother-infant pairs of fulminant hepatitis B. Eight mother-infant pairs were subjected to viral load and genotype analysis by real-time PCR assay (table 6). The viral load of patients ranged from $1.8x\ 10^4$ to 1.9×10^8 copies/mL; the viral load of mothers ranged from 2.3×10^3 to 8.7×10^7 copies/mL. In all but one pair, patient's viral load was higher than mother's viral load. There was no correlation between patient's viral load and prognosis. The genotype was all B except on patient who was mixed B and C type.

討論

This study revealed that after implementation of universal vaccination, HBV related FHF had not been eradicated. Age was an important factor affecting the incidence of FHF. Although HBV-positive FHF had been rare in children aged one year and up, it still persisted as the major cause of FHF in infants below one year of age. Fifty-seven percent of all the infant cases of FHF could be attributed to HBV infection; this rate had been lower than the rate before the hepatitis B vaccination program was implemented (82%).10

The age distribution of pediatric fulminant hepatic failure had not been well defined. We have shown in this study that the incidence of FHF was much higher in infants (1.29 per 100,000) than in children aged one to 15 years (0.053 per 100,000). The definition of FHF in infants might be different from that for the adult population, since encephalopathy can be absent or difficult to diagnose in infants, and since acute liver failure can cause death without overt symptoms of encephalopathy. Therefore, the actual number of infant cases could be higher than reported.

Previous reports had observed a infant preponderance (36% to 65% of all pediatric cases) of FHF caused by HBV.10,34 It is noteworthy that in the present study, the infant preponderance was more exaggerated in HBV-positive cases than in HBV-negative cases. The incidence rate

ratio of infants below one year to children one to 15 years was 54.2 in the HBV-positive group compared with 15.2 in the HBV-negative group. It is well recognized that fulminant hepatitis B develops in primarily two groups of patients with different sources of infections. One of such occurs in infancy, acquiring the infection from their mothers, and has a peak onset age of three to six months; the other occurs at a later age via a horizontal route, i.e., blood transfusion.10,34 Cases caused by horizontal infection could also be prevented by blood product screening.

Limitations of this study included incomplete vaccination records and maternal HBsAg/HBeAg status. Despite that four of the 43 HBV-positive patients did not have a HBV vaccination record, the majority of children acquiring HBV-positive FHF in the post-vaccination era had received vaccinations appropriate for their ages. However, many infant (23/25) cases developed FHF before the age of six months, i.e., before completion of a full course of vaccination. Development of HBV-positive FHF earlier than the age when full protection from vaccination can be achieved is possible. The question of whether infants born to HBsAg-positive/HBeAg-negative mothers were at higher risk of developing FHF deserves further investigation. Before the universal vaccination program, we had observed that FHF caused by HBV occurred particularly in infants born to HBeAg-negative, HBsAg-carrier mothers.10,19,20 In the present study, this trend still present. This result is biased since the vaccination program only administered HBIG to infants born of HBeAg-positive mothers; and only 25 of 33 HBV-positive infants had maternal HBeAg/anti-HBe data. It could be possible that vaccination alone was not effective in preventing HBV infection in these children who did not receive HBIG. On the other hand, we and other investigators have observed fulminant hepatitis B in infants despite appropriate prophylaxis of HBIG and HBV vaccines.35 Previous studies have shown that under the present vaccination program, 1% to 3% of the infants born to HBeAg-negative, HBsAg-carrier mothers and 3.3% to 7.4% of infants born to HBeAg-positive, HBsAg-carrier mothers became HBsAg carriers.23, 36 37 The risk of developing FHF in these infants was unknown.

Our study did not provide direct evidence that vaccination had reduced the incidence of HBV-induced FHF in children. Nevertheless, indirect evidence was provided by the Nationwide Mortality Registry Database showing that in infants below one year of age, the yearly mortality rates from hepatitis had decreased from 5.36 to 1.71 per 100,000 in the years 1975 to 1984 and 1985 to 1998.30 We also showed in this study that in children aged one to 15 years, the annual mortality rate had decreased from 0.27 to 0.10 per 100,000. The decrease in cases was also supported by the percentage of HBV-related cases in infants and children, which was 57% and 27% in this study, compared to the previous study of 82% and 67% before the vaccination program.10 Even though the mortality database recruited patients with hepatitis due to all causes, the source of the reduction was most likely due to the decrease of HBV-positive FHF cases.

Male predominance has been well documented in HCC.38 It has also been demonstrated that the decrement of childhood HCC after universal vaccination was more significant in males than in females.39 In the present study, male preponderance was only significant in infants with HBV-positive FHF, and not significant in HBV-negative FHF or in the age group of one year or older. The reason remains to be clarified.

Many scores to predict prognosis in either FHF or chronic liver failure have been proposed to determine the optimal timing and candidate for liver transplantation. In the present study, we found that HBV-positive and -negative cases differed in clinical features and outcomes. Hepatitis B viurs-positive cases had more favorable outcomes than HBV-negative cases. Moreover, the risk factors affecting mortality were different in HBV-positive and -negative groups. The age of HBV-positive FHF patients was younger (1.8 ± 3.5 *vs* 3.8 ± 4.4 years), probably because many HBV-positive FHF cases were infected perinatally from their HBsAg carrier mothers.

In HBV-positive cases, the most important factor for the outcome is prolonged PT.

Prothrombin time is the most sensitive measure of the hepatic synthesis of clotting factors and depends on Factor VII, which decreases more rapidly than other liver-derived clotting factors for its short half-life.[20] Marked coagulopathy (PT ≥ 40 s) increased the risk of bleeding, especially intracranial hemorrhage. A previous study reported that a prolonged PT ≥ 50 s correlated with the degree of necrosis, but did not necessarily indicate a fatal outcome.[60]

Hepatitis B virus-negative FHF tended to have higher bilirubin levels than HBV-positive cases did. Two main factors were found to affect the outcome in our series: age and serum total bilirubin level. Multivariate analysis revealed that bilirubin levels were the only factors affecting the outcome. Conjugated bilirubin levels in our series showed no significant relationship to mortality, probably because of the unconjugated form being the main form of bilirubin at the later stage of FHF, indicating the loss of conjugation function of hepatocytes. Furthermore, PT was not a significant factor in the HBV-negative group. We speculated that the majority of HBV-negative cases had longer PT levels. Thus, in more severe cases, PT could not distinguish between cases with or without regeneration activity.

There have been reports on the factors predicting outcome in pediatric FHF patients. These studies were conducted mostly in non-HBV cases. Ventilator dependency prior to transplantation has been suggested to be the strongest predictor of survival, particularly in those younger than 4 years of age.[55] Neurological findings and multiple organ failure have also been suggested to be the most consistent discriminators for transplantation and outcome.[56] Bilirubin, INR, albumin, growth failure, and age had been used as a pediatric end-stage liver disease score for children with chronic liver disease to prioritize children awaiting liver transplantation.[61] These reports were conducted in pooled patients with different etiologic backgrounds.

The pediatric risk of mortality (PRISM) was likewise used for assessing the severity of pediatric FHF.[62] Significant differences were observed between children who spontaneously recovered with supportive care and those who underwent emergency liver transplantation or those who died before. However, PRISM score-based probability was underestimated when compared with observed mortality. A better understanding of the parameters that affect the outcome would greatly aid in the decision on transplantation for a specific patient.

It is interesting to note that in the present study, there was a trend of decreasing mortality in HBV-positive cases in the past 15 years. Whether the universal HBV vaccination program affected the disease course deserved further investigation. We observed the trend that the percentage of patients in the group of PT > 50 s decreased gradually (97, 67 and 55%). If the improvement in survival rate was because of the decreased severity of the disease related to vaccination or because of the improvement of intensive care, remains unclear. In contrast, given that the quality of intensive care was similar in the same period of time, liver injury in HBV-negative cases might be so severe that supportive care had limited value in improving the survival rate, with liver replacement therapy being the only alternative.

In conclusion, within the first 15 years of universal vaccination, HBV was rarely the cause of FHF in children above one year in age, while it remained a major cause of FHF in infants. These infants were most likely infected perinatally from their HBeAg-negative, HBsAg-carrier mothers. Under the vaccination program in place during this study, only HBV vaccines, and not HBIG, were given to those infants. Administration of HBIG to all infants born of HBsAg-positive mothers might be considered, and the effect this has on preventing infant FHF deserves further investigation. In addition, we found that HBV-negative FHF cases had a higher mortality rate than the HBV-positive cases. Prothrombin time was the main factor affecting outcome of HBV-positive FHF. Finally, higher peak total bilirubin levels were associated with higher mortalities in the HBV-negative group.

Table 1. Incidence rates and rate ratios between age groups of HBV-positive fulminant hepatic failure (FHF) and HBV-negative FHF within the 15 years of the universal vaccination program.

	Year 1985-1999	IRR (<1yr vs 1-15yr)	*p*-value
	Case no. (incidence per 100,000)	[95% C.I.]	
HBV (+) FHF	43		
<1 yr	33(0.74)	54.2	<0.01
		[26.1, 123.2]	
1-15 yr	10(0.014)		
HBV (-) FHF	52		
<1 yr	25(0.56)	15.2	<0.01
		[8.5, 27.2]	
1-15 yr	27(0.039)		

Total person-years: 0-5 yrs: 73,580,339; 0-1 yrs: 4484057; 1-15 yrs: 69096282.

IRR: incidence rate ratio.

Table 2. Gender differences in the incidence of HBV positive and negative FHF in different age groups.

	Male Case no. (incidence per 100,000)	Female Case no. (incidence per 100,000)	IRR (male vs female) [95% confidence interval]	*p*-value
HBV (+) FHF				
<1 yr	25 (1.07)	8 (0.37)	2.88 [1.30, 6.39]	0.009
1-15 yr	6 (0.017)	4 (0.012)	1.40 [0.39, 5.00]	0.60
HBV (-) FHF				
<1 yr	16 (0.69)	9 (0.42)	1.64 [0.72, 3.71]	0.24
1-15 yr	15 (0.042)	12 (0.036)	1.17 [0.55, 2.49]	0.69

IRR: incidence rate ratio.

Table 3 Clinical characteristics of survival and mortality groups in fulminant hepatitis in children

	FHF cases (n = 94)	Survival cases (n = 24)	Mortality cases (n = 70)	P	
Age (years/old)	2.9 ± 4.1	0.9 ± 1.4	3.6 ± 4.5	<0.001*	
Peak total bilirubin (umol/L)		466.8 ± 256.5	323.2 ± 186.4	514.7 ± 275.3	0.003*
Peak direct bilirubin (umol/L)		212.0 ± 179.6	167.6 ± 99.2	225.7 ± 196.7	0.213
Peak AST (U/L)	2352 ± 2551.5	3224 ± 3613.1	2030 ± 1967.2	0.136	
Peak ALT (U/L)	1737 ± 1913.3	2257 ± 2266.7	1569 ± 1774.3	0.174	
Prothrombin time (≥50 s)		71% (57/80)	52% (12/23)	79% (44/57)	0.027*
HBV positive	45% (42/94)	63%(15/24)	39%(27/70)	0.042*	

Data expressed as mean ± SD; *Statistically significant (P < 0.05). ALT, alanine aminotransferase; AST, aspartate aminotransferase; FHF, fulminant hepatic failure; HBV, hepatitis C virus.

Table 4 Clinical characteristics in the survival and mortality group of HBV positive and HBV negative fulminant hepatitis

	HBV positive	HBV negative	*P1*			HBV positive		HBV positive	*P2*	HBV negative	HBV negative	*P*3
	(*n* = 42)	(*n* = 52)		survival (*n* = 15)		mortality (*n* = 27)			survival (*n* = 9)	mortality (*n* = 43)		
Age (y/o)	1.8 ± 3.5	3.8 ± 4.4	0.004*	0.88 ± 0.45	2.37 ± 0.79	0.11	0.9 ± 0.6	4.3 ± 4.7	<0.001*			
Peak total bilirubin (umol/L)	282.2 ± 148.8	400.1 ± 208.6 584.8 ± 290.7	0.006*	535.2 ± 294.1	0.006*	345.4 ± 53.0		403.6 ± 41.0	0.399			
Peak direct bilirubin (umol/L)	147.1 ± 80.37	153.9 ± 111.2 280.4 ± 220.6	0.007*	256.5 ± 208.6	0.101	183.0 ± 32.5		140.2 ± 22.2	0.291			
Peak AST (U/L)	2484 ± 2029	2258 ± 2882	0.664	2926.2 ± 629.4		2183.3 ± 360.8		0.28				
Peak ALT (U/L)	3719 ± 5166.4	1952 ± 2108.7	0.341									
Prothrombin time (s)	2155 ± 2151	1413 ± 1261	0.101	1709.5 ± 379	2398.4 ± 530.4	0.38	3197 ± 3259.3	1076 ± 889.1	0.137			
	73.7 ± 46.7	56.7 ± 23.3	0.96	54.1 ± 8.6	88.2 ± 11.7	0.036*	51.4 ± 29.8	57.9 ± 21.8	0.458			

P1, comparison between HBV positive and HBV negative cases; *P2*, comparison between survival and mortality cases in HBV positive group; *P3*, comparison between survival and mortality cases in HBV negative group; Data expressed as mean ± SD; *Statistically significant ($P < 0.05$). ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis C virus.

Table 5 Changes of mortality rate in fulminant hepatitis in a 15-year period (1985–1999)

Years	1985–1989		1990–1995	1995–1999	*P*
FHF (no.)	27	30	37		
Mortality (no.)	21	23	26		
Mortality rate (%)	78	77	70	0.75	
HBV fulminant (no.)	11	18	13		
Mortality (no.)	10	12	5		
Mortality rate (%)	91	67	38	0.027*	
PT prolonged ≥50 s (%)		90	67	55	0.084
Non-HBV fulminant (no.)		16	12	24	
Mortality (no.)	11	11	21		
Mortality rate (%)	69	92	88	0.198	
PT prolonged ≥50 s (%)		64	73	73	0.846

Data expressed as mean ± SD; *Statistically significant ($P < 0.05$). FHF, fulminant hepatic failure; HBV, hepatitis B virus; PT, prothrombin time.

Table 6. Viral load (copies/mL) and genotype of mother-infant pairs of fulminant hepatitis B

Patient No.	Patient viral load	Mother viral load	Patient genotype	Prognosis
1	2.5×10^4	5.2×10^3	B/B	M
2	4.4×10^4	2.3×10^3	B/B	M
3	1.9×10^8	1.3×10^4	B/B	M
4	4.8×10^4	8.7×10^7	B/B	M
5	1.8×10^4	8.7×10^3	B/B	1
6	4.6×10^6	ND	B/ND	1
7	1.3×10^7	4.4×10^4	B+C/B	1
8	1.7×10^8	6.5×10^4	B/B	1

ND: not detectable; A: alive; M: mortality

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