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ORIGINAL ARTICLE

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The effect of hepatitis B vaccination on the incidence of childhood HBV-associated nephritis

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Abstract The aim of the present study was to investigate the effect of a vaccination program for hepatitis B virus (HBV) on the incidence of HBV-associated glomerulonephritis (HBV-GN). In total, 727 renal biopsies were carried out at our hospital from November 1979 through March 2002. Two groups were established. Group A included those biopsied from November 1979 through December 1991 (prior to the HBV vaccination program) and group B from January 1992 through March 2002. Group B was divided into five subgroups (B_1 to B_5), with an interval of 2 years between each subgroup. Patients were divided into those with or without a history of HBV vaccination. Of the 727 renal biopsies, 64 fulfilled the criteria of HBV-GN, There were 28 cases of the 211 cases in group A and 36 cases of the 516 cases in group B (X^2=7.397, P<0.01). The incidence in group A and group B_1 through B_5 was 13.27% (28/211), 13.04% (9/69), 7.32 (6/82), 6.25% (4/64), 4.88% (4/82), and 5.94% (13/219), respectively (X^2=9.627, P<0.01). Only 8 of the 231 vaccinated children had HBV-GN, while there were 48 HBV-GN cases of the 381 non-vaccinated children (X^2=14.44, P<0.001). There were only 6 cases of membranous nephropathy (MN) in the vaccinated group, while 40 cases of MN occurred in the non-vaccinated group (X^2=12.92, P<0.01). There were 8 children that developed HBV-GN with abnormal serum HBV markers despite HBV vaccination. Two mothers of these 8 children had evidence of HBV infection. The incidence of HBV-GN in children has been decreasing each year since the implementation of the nationwide HBV vaccination program in Shanghai, China. Furthermore, since childhood MN is associated with HBV, vaccination can also reduce the incidence of childhood MN.

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Introduction

Childhood hepatitis B virus-associated glomerulonephritis (HBV-GN) is one of the major causes of secondary renal damage in children; its pathological pattern is mainly membranous nephropathy (MN). Studies have confirmed that an HBV vaccination program has brought the HBV epidemic under control. However, there has been no report on the effect of vaccination on the incidence of HBV-GN. In this retrospective study we evaluated the impact of HBV vaccination on the incidence of HBV-GN diagnosed at Fudan University in Shanghai, China.

Materials and methods

There were 727 transcutaneous renal biopsies with complete clinical data performed at Children's Hospital, Fudan University, Shanghai, China from November 1979 through March 2002. Two groups were established. Group A (211 cases) included those biopsied from November 1979 through December 1991 (prior to the HBV vaccination program). Group B (516 cases) included those biopsied from January 1992 through March 2002. Group B was further subdivided into five subgroups (group B_1 to group B_5) with an interval of 2 years between each. They were group B_1: 1992–1993 (69 cases), group B_2: 1994–1995 (82 cases), group B_3: 1996–1997 (64 cases), group B_4: 1998–1999 (82), and group B_5: 2000–2002 (219). Patients were divided into those with (231 cases) and without (381 cases) a history of HBV vaccination. The vaccination history was unclear in the remaining 115 cases.

The presence of HBV markers was determined with ELISA kits. The renal tissue samples obtained by transcutaneous renal biopsy under the guidance of B scan ultrasonography were examined by light, immunofluorescence (including IgG, IgA, IgM, C3, and HbsAg), and electron microscopy. Immunohistochemical analysis (HBcAg, HBsAg) and HBV DNA analysis were performed in 48 cases.

Diagnostic criteria for HBV-GN were according to those (Beijing) drafted at the National Symposium on Hepatitis B Virus Associated Glomerulonephritis in 1997 [1]. The criteria included: (1) positive serum HBV markers, (2) renal parenchymal damage,

Table 1 Incidence of childhood hepatitis B virus-associated glomerulonephritis (HBV-GN)

	HBV-GN (*n*)	Non-HBV-GN (*n*)	Renal biopsy (*n*)
Group A (*n*) 1979–1991	28	183	211
Group B (*n*) 1992 to March 2002	36	480	516
Total (*n*)	64	663	727

X^2=7.39, **P*<0.01

Table 2 Vaccination with HBV vaccine and the incidence of childhood HBV-GN

	HBV-GN (*n*)	Non-HBV-GN (*n*)	Total (*n*)
Vaccinated group	8	223	231
Non-vaccinated group	48	333	381
Total (*n*)	56	556	612

X^2=14.44, **P*<0.001

hematuria, and/or proteinuria, exclusion of other secondary nephropathy, such as lupus nephritis, purpura nephritis, and diabetic nephropathy, (3) HBV antigen in the renal pathological section and/or positive HBV DNA, and (4) major pathological changes of MN.

Statistics

X^2 testing and SAS6.12 software were used for the analysis of all the data.

Results

HBV-GN was diagnosed in 64 (8.80%) of the 727 cases with renal biopsies. There were 58 males and 6 females. The age at onset ranged from 2 years, 6 months to 11 years, 9 months (mean 7.03±2.65 years); the interval between the onset of symptoms and renal biopsy ranged from 1.5 months to 10 years (mean 12.46 months), and the age at renal biopsy ranged from 2 years, 6 months to 15 years (mean 8.07±2.91 years). All 64 cases were positive for serum HBV markers.

The number of glomeruli in the biopsy specimens ranged from 1 to 80 (mean 17±13). In 95% of biopsies there were more than 6 glomeruli each (61/64). Of the remaining 5 cases, 1 had 5 glomeruli, 4 had only 1 (HBV DNA was detected in the 4 biopsy samples).

There were 46 cases of MN among the 64 cases of HBV-GN. There were 18 cases with other patterns, with membranous proliferative nephritis in 6 cases, mesangioproliferative nephritis in 7 cases, minimal lesion nephropathy in 4 cases, and focal segmental sclerotic glomerular nephritis in 1 case. HBV antigen and/or HBV DNA in the renal tissue were found in these 18 cases and 30 cases of MN (30/46).

Table 1 shows the incidence of HBV-GN before and after 1992. HBV-GN was diagnosed in 28 (13.27%) of the 211 cases in group A, while in the 516 cases of group B, 36 cases (6.98%) were diagnosed as HBV-GN (significant difference statistically). The incidence of HBV-GN in group B was markedly lower than that of group A. Figure 1 shows the change in the incidence of HBV-GN.

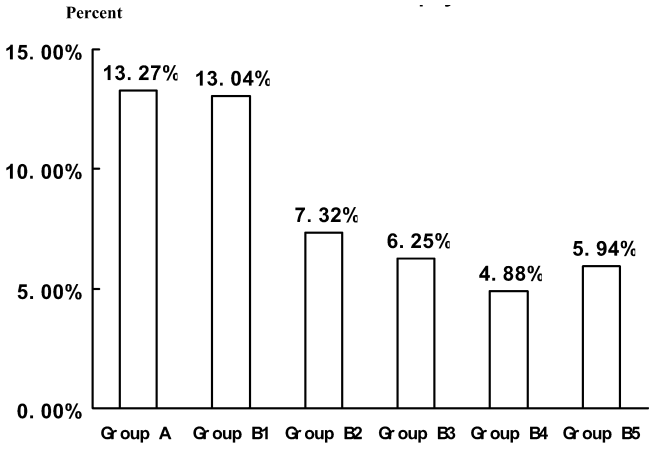

Fig. 1 The incidence of hepatitis B virus-associated glomerulonephritis (HBV-GN) in patients with renal biopsies. X^2=9.627, **P*<0.01. Group B_1 1992–1993, group B_2 1994–1995, group B_3 1996–1997, group B_4 1998–1999, group B_5 2000–2002

The incidence in group A and group B_1 to B_5 was 13.27% (28/211), 13.04% (9/69), 7.32% (6/82), 6.25% (4/64), 4.88% (4/82), and 5.95% (13/219), respectively, with a significant difference indicating a decreasing incidence.

Table 2 shows the incidence of childhood HBV-GN in both the vaccinated and non-vaccinated children (total 727). Only 8 cases (3.46%) of HBV-GN were seen in 231 vaccinated children, while 48 cases (12.60%) of HBV-GN occurred in 381 non-vaccinated children. The incidence of HBV-GN in the vaccinated group was significantly lower than in the non-vaccinated group.

All 46 cases of MN were HBV-GN (6.33%). Table 3 shows the relationship between the incidence of childhood MN and HBV vaccination. There were only 6 cases of MN (2.60%) in the vaccinated group, while there were 40 cases (10.50%) in the non-vaccinated group. The incidence of MN in the vaccinated group was significantly lower than in the non-vaccinated group. Figure 2 shows the incidence of MN before and after1992.

Table 3 Vaccination with HBV vaccine and the incidence of childhood membranous nephropathy (MN)

	MN (*n*)	Non-MN (*n*)	Total (*n*)
Vaccinated group	6	223	231
Non-vaccinated group	40	341	381
Total (*n*)	46	566	612

X^2=12.92, **P*<0.001

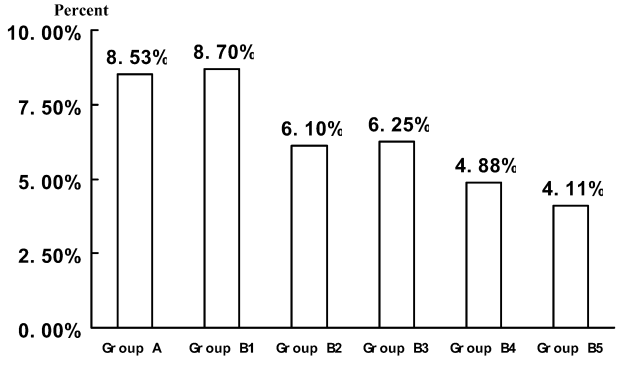

Fig. 2 The incidence of membranous nephropathy (MN) in patients with renal biopsies. X^2=4.49, **P*>0.05. Group B_1 1992–1993, group B_2 1994–1995, group B_3 1996–1997, group B_4 1998–1999, group B_5 2000–2002

There were 8 children who developed HBV-GN despite vaccination; all showed positive serum HBV markers. The mothers of 2 children who developed MN were identified as having HBV infection. HBV antigen and antibody were not tested in the remaining 6 mothers of these children with HBV-GN.

Discussion

As HBV is endemic in China, great attention has been paid to HBV-GN. HBV vaccination is the most effective means of preventing the spread of HBV. Routine neonatal HBV vaccination has been performed in parts of China since the middle 1980s. Routine neonatal HBV vaccination is part of the vaccination program for children in the Nanshi Prefecture of Shanghai. Studies have shown that routine HBV vaccination of neonates can greatly reduce the carrier rate of HBsAg and the infection rate of HBV in the population. The infection rate was reduced by more than 95% in the 3- to 8-year age group and 92.23% in the 1- to 2-year age group [2, 3]. Since 1 January 1992, routine HBV vaccination has been implemented nationwide in China. The infection rate of HBV in children has been reduced to below 0.5%.

Can HBV vaccination reduce the incidence of HBV-GN in children? We grouped our patients according to the time of introduction of nationwide HBV vaccination in order to investigate the effect of vaccination on the incidence of HBV-GN. The incidence of HBV-GN before and after 1992 was 13.27% and 6.98%, respectively. The difference is significant statistically, and there is an annual downward trend in incidence after 1992. The incidence of HBV-GN increased slightly during 2000–2002 (B_5 group). The reason for this is unknown and needs further investigation.

With the increasing acceptance of renal biopsy by parents of patients, the number of renal biopsies performed annually has also been increasing. Thus we studied the HBV vaccination status in children with HBV-GN. Most of the children with HBV-GN (87.5%) had not been vaccinated. The incidence of HBV-GN in the vaccinated group was significantly lower than in the non-vaccinated group, demonstrating that the incidence of HBV-GN in children has decreased significantly since the introduction of the nationwide HBV vaccination program in 1992.

It is well known that primary MN in children is rare. Most cases of childhood MN are associated with HBV-GN; therefore, cases of nephrotic syndrome or glomerulonephritis with positive serum HBV markers and MN can still be diagnosed as HBV-GN, despite negative results for HBV markers in renal tissues [4]. All the 46 cases of MN (6.33%, 46/727) in the present series of 727 renal biopsies were associated with HBV-GN (71.875%, 46/64), further demonstrating that most childhood MN is associated with HBV-GN and primary MN is rare. The incidence of MN in the vaccinated group was significantly lower than in the non-vaccinated group. Therefore, with routine HBV vaccination, the incidence of childhood MN is also reduced, and is decreasing annually (although without statistical significance at present).

HBV-GN still occurred in some patients who had been vaccinated with HBV vaccine. We discovered evidence of infection with HBV in 2 mothers of these children. It has been confirmed that multiple injections of HBIG to mothers carrying HBV can effectively reduce intrauterine infection with HBV [5, 6]. Thus, HBV screening during pregnancy is very important. Combining HBIG with vaccine is important in preventing maternal-infant transmission of HBV. Therefore, serological follow-up after HBV vaccination should be rigorously performed for high-risk children, to identify failure of immunization earlier and to offer appropriate intervention.

Review of the literature did not uncover any similar report. We are the first to report that the incidence of HBV-GN in children has been significantly reduced, and has been decreasing annually in Shanghai, China, after the introduction of the nationwide HBV vaccination program. Furthermore, since childhood MN is associated with HBV, routine HBV vaccination should reduce the incidence of childhood MN.

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