The Prevalence and Its Meaning of Anti-HBc Alone 15 Years Subsequent to Mass Hepatitis B Vaccination

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Abstract

Fifteen years subsequent to nation-wide mass hepatitis B vaccination program, the prevalence of anti-HBc and HBsAg among adolescents/children in Taiwan has decreased. The significance of anti-HBc alone among the vaccinees-cohort has not been determined as yet. The aims of this study were to investigate the prevalence and its meaning of anti-HBc alone among vaccinees-cohort based upon a battery of strategies, including evaluating the response to the hepatitis B vaccine booster, assessing tests for anti-HBe, and determining the viral load by use of a sensitive real-time polymerase chain reaction assay. Adolescents born after mass vaccination program being instituted and aged between 12 and 15 years in one rural township of Taiwan were selected as the studied population. The vaccination coverage rate during infancy was 72.4% (312/431). The seroprevalence of anti-HBc and HBsAg was, respectively, 19.5% (219/1,126) and 7.1% (80/1,126). The prevalence of anti-HBc alone was 0.9% (10/1,126). Five of these ten anti-HBc alone subjects were positive for anti-HBe; among them, three have anti-HBs anamnestic response after hepatitis B vaccine booster (ie, past resolved HBV infection), the other two without anti-HBs anamnestic response were thought to be HBV carrier (including one case with HBV DNA positive and viral load 281 copies/ml). One case that was negative anti-HBe result and had no anamnestic response was invited to complete HBV vaccination; and primary response was deduced. Therefore, anti-HBc of this case was assumed as false positive. Another one whose anti-HBc turned to be negative on follow-up sampling. Hence, his initial anti-HBc was also thought to be false positive. The last three complete vaccinated and negative anti-HBe cases could not be accurately differentiated as true positive as opposed to false positive. In conclusion, the prevalence of anti-HBc alone was 0.9% among vaccinees-cohort. One half of isolated anti-HBc subjects revealed that they were true positives, and viremia did occur for one case.   (J Intern Med Taiwan 2002;13: 247-255)

Key Words：Hepatitis B, Vaccine, Real time PCR, Anti-HBc, Anti-HBc alone,
            Occult HBV infection

Introduction

The presence of antibodies against the core antigen of hepatitis B virus (anti-HBc), as detected by enzyme immunoassay (EIA), and representing the only seromarker for hepatitis B is not a common occurrence, and the significance of such a scenario remains uncertain. There are four possible explanations for such a situation 1. Firstly, a small proportion of isolated anti-HBc cases is assumed to represent individuals in the acute diagnostic window phase when hepatitis B surface antigen (HBsAg) has disappeared following infection and prior to antibodies to hepatitis B surface antigen (anti-HBs) becoming detectable, during which period anti-HBc IgM is detectable. Secondly, the absence of HBsAg for subjects with isolated anti-HBc results from either the suppression of hepatitis B virus (HBV) replication or HBsAg expression/secretion. In such a situation for a subject, a low viremia status or a chronic carrier status remains a possibility. Thirdly, isolated anti-HBc can also reflect a phase of late immunity, often many years subsequent to the resolution of the original infection, at which time anti-HBs have fallen below detectable levels. Finally, there may exist a non-specific cross-reacting antibody (i.e. false positive for anti-HBc). Taiwan has long been a HBV-endemic area, and, previously, the positive rate of the presence of serum anti-HBc was near 80-90% and the carrier rate of HBsAg in the population has reached a level as high as 15-20% prior to the nationwide hepatitis B mass vaccination program being instituted 2. In order to control this serious public-health problem in Taiwan, a mass immunization program against hepatitis B was launched on July 1, 1984, one of the earliest such national immunization programs in the world 3-7. Fifteen years subsequent to this mass vaccination program, the prevalence of anti-HBc and HBsAg amongst adolescents/children living in the Taipei metropolis was only around 2.9% and 0.7%, respectively 4.

The prevalence of anti-HBc alone has been found to range from ten to fifteen percent among adult individuals in Taiwan 8-9. Following mass immunization, the prevalence of anti-HBc alone has decreased to 0.3% among children who have received a complete course of vaccination 5, although, the meanings of anti-HBc antibody for these vaccinees with isolated anti-HBc have not been determined to date. The aims of this study were to investigate the significance of isolated anti-HBc among a vaccinees-cohort some fifteen years subsequent to a mass vaccination program. This study was based upon a battery of strategies, including evaluating the response to a hepatitis B vaccine booster, the assessment of antibodies against HBV e antigen (anti-HBe) status, and the determination of the viral load by

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use of a sensitive, real-time polymerase chain reaction (PCR) assay. We selected the adolescent students of one junior high school in a rural township to constitute our studied population.

Materials and Methods

National vaccination program

The national program of universal HBV vaccination in Taiwan commenced on July 1, 1984 3-7, at which time, only the newborn infants of mothers who were HBsAg carriers were being vaccinated. The vaccination program was extended in July 1986 to include all newborn infants and in July 1987 to cover all children of preschool age. Infants were originally given a 5μg dose of plasma-derived hepatitis B vaccine (Hevac B, Pasteur Institute, Marnes-la-Coquette, France) at birth and one, two and 12 months of age. In addition, 0.5 mL (145 IU) of hepatitis B immunoglobulin was given within 24 hours of birth to those infants whose mother had hepatitis B e antigen or reciprocal serum HBsAg titers of 2560 or more. Subsequent to November 1992, the plasma-derived vaccine was replaced by a recombinant yeast vaccine with a three-dose regimen at ages zero, one, and six months. The details of this vaccination program have been described elsewhere 7.

Background data and demographics of the   studied township

Taishi Township, a rural township belonging to Yunlin County, which is located at the central-south part and the western coast of Taiwan, was selected as the study site. Around half of the township's population is engaged in farming. According to the previous seroprevalence study (surveyed in July 1, 1984 through to September 30, 1985) conducted by the Science and Technology Advisory Group and the Department of Health of Taiwan, the prevalence of HBsAg and of highly-infectious carriers (defined as a positive HBeAg or a reciprocal HBsAg titer of 2560 or more by reversed passive hemagglutination test) amongst pregnant women in Yunlin County was 20% (2,664/13,418) and 43% (1,144/2,664) respectively 7.

This study was conducted in March 1999 through to March 2001 and enrolled students aged from 12 to 15 years from the solitary junior high school in Taishi Township. A total of 1,126 adolescents who were born in July 1984 through to December 1989 inclusively were selected, this subpopulation comprising 93.9% of adolescents of this age group from this junior high school. Informed consents were obtained from all participating students parents. Thus, the study subjects represented a cohort of individuals who participated in the first five years of the nation-wide hepatitis B vaccination program. We further divided these individuals into two groups by birth cohort: group A included 425 subjects born between July 1984 and Jun 1986 inclusively, when the immunization program covered only newborn infants born to HBsAg carrier mothers, and, group B which included 701 subjects born between July

1986 and December 1989 inclusively, at which time all infants were vaccinated.

Vaccination histories

We checked all official vaccination records of

studied subjects during infancy from the Taishi Health Station. Subsequent to July 1986, at which time the vaccination program was extended to all newborns, trained nurses from the Taishi Health Station began to record the official vaccination histories faithfully and rigorously. Therefore, only students deriving from group B were able to demonstrate available official vaccination records, this not being the case for students constituting group A. Further, approximately 40% of students attending this school were born in neighboring townships and moved into Taishi Township later, such that the vaccination hi-

stories of these immigrant students were not also available. Complete vaccination was defined as a subject receiving three or four doses of vaccines. Incomplete vaccination was defined as a subject receiving two or fewer doses of vaccines. The vaccination coverage rate was defined as the ratio of those who received complete vaccination to all subjects.

Seroprevalence of HBV infection

All studied individuals received tests for the

presence of HBsAg, anti-HBs and anti-HBc using commercial enzyme immunoassay (AxSYM, Abbott, North Chicago, IL, USA). The value of anti-HBc (AxSYM CORE, Assay Number 126) is considered as positive if S/CO (sample rate/cutoff rate) lies in the range of 0.000 to 1.000, and is classified as negative if the value lies in the range of 1.001 to 3.000. Samples with anti-HBs (AxSYM AUSAB) less than 10 mIU/mL are interpreted as nonreactive.

Strategies applied to define the nature of anti-HBc amongst anti-HBc alone subjects

For those individuals revealing isolated anti-HBc, all received repeated HBsAg and anti-HBc tests at least three months apart. An inconsistent result for anti-HBc (i.e. the loss of anti-HBc in the follow-up sampling) was defined as a false positive anti-HBc reading initially. We performed tests for anti-HBe

status (AxSYM, Abbott), and also HBV DNA assay (by a real-time PCR process, see below) in order to look for any evidence of HBV exposure. Tests for the presence of anti-HBc IgM were conducted in order to rule out the potential for acute HBV infection. All isolated anti-HBc individuals were invited to receive a hepatitis B vaccine booster (Engerix-B 20 microgram/1mL; SmithKline Beecham, Rixensart, Belgium). We checked the anti-HBs response one month following the vaccine booster. An anamnestic response was defined as an anti-HBs titer greater than 50 mIU/mL following the vaccine booster 10-11. If

studied subjects revealed any evidence of existing HBV infection (positive anti-HBe

and/or HBV DNA tests) but demonstrated no anamnestic response, they were arbitrarily classified as HBV carriers with undetectable HBsAg 1,12. For individuals who exhibited neither an anamnestic response nor any evidences of HBV infection, a complete course of additional two doses (second dose at one month, and third dose at six months) with recombinant yeast vaccines were suggested. The titer of anti-HBs $\geqq$ 10 mIU/mL 1 month after the third dose vaccine was defined as primary response. If such a primary response was disclosed, his anti-HBc was defined as false-positive result 10-11. To rule out a possible suppressive role of he-patitis C virus (HCV) infection, all study subjects underwent third generation anti-HCV antibody tests (AxSYM, Abbott).

Real-time PCR

Separated subjects sera were snap frozen at -70℃ until time of use. HBV DNA was extracted from serum (a total 400 microliter) using the QIAamp DNA mini kit (Qiagen Ltd., Crawley, United Kingdom). The Qgene Detector System TM performs real-time pro-duct detection using GeneAmp 5700 instrument. The Qgene HBV Detector TM Assay system (Qgene Biotech. SF, USA) was amplified from HBV core region and used to quantitate the level of HBV DNA in serum (with a sensitivity of 20 copies/ml).

Statistical analyses

Any differences in the determined frequencies between different groups were examined using chi-square test with Yates correction. A P value of less than 0.05 for any comparison of sample means was considered to constitute a significant difference between samples.

Results

Vaccination histories

A total of 431 individuals from group B who resided in Taishi Township from the time of their birth to the time of this study revealed available vaccination records, from which we noted that 72.4% (312/431) of these individuals received three or four doses of vaccine (complete vaccination), and 27.6% (119/431) received two or fewer vaccines (incomplete vaccination; Table 1).

Seroprevalence of HBV among studied adolescents

In total, the seroprevalence for anti-HBc and HBsAg among study participants was 19.5% (219/1,126) and 7.1% (80/1,126) respectively (Table 2). Among such individuals, ten cases proved to be anti-HBc alone (0.9%, 10/1,126): two belonged to group A and eight were classified into group B. The prevalence of a positive anti-HBc amongst group A members appeared to be greater than the analogous figure for group B (30.8% [131/425] vs. 12.6% [88/701] respectively, p < 0.001; Table 2). The seroprevalence of HBsAg for group A members

was also greater than the analogous figure for group B (11.5% [49/425] vs. 4.4% [31/701], p < 0.001; Table 2). For subjects who possessed available vaccination histories, individuals who received incomplete vaccination revealed a greater prevalence of anti-HBc than was the case for those individuals reflecting complete vaccination record (16.0% [19/119] vs. 10.3% [32/312], p = 0.132; Table1). Similarly, individuals who received an incomplete vaccination revealed a greater prevalence of HBsAg than was the case for complete vaccinees (5.9% [7/119] vs. 3.5% [11/312], p = 0.287; Table 1), although such comparisons demonstrated no statistical significance. The seroprevalence of anti-HBc and HBsAg among individuals with known and unknown vaccination histories appeared not to differ (11.8% [51/431] vs. 13.7% [37/270] respectively, p=0.484; and 3.7% [16/431] vs. 5.6% [15/270], p=0.262; Table 1).

The significance/meanings of anti-HBc among anti-HBc alone subjects (Table 3)

Ten cases proved to be anti-HBc alone, all of which revealed the absence of anti-HCV antibodies, and the absence of any positive anti-HBc IgM results. Repeated HBsAg tests were done and all these ten cases exhibited negative HBsAg results on follow-up samples.

Five cases revealed positive anti-HBe results (cases 1-5), therefore their anti-HBc were thought to be true positive; and one of them exhibited Z-le-vel viremia (case 1; viral load of HBV DNA was 281 copies/mL), hence, occult HBV infection was defined for case 1.

Seven anti-HBc alone subjects demonstrated an anamnestic anti-HBs response subsequent to a vaccine booster (cases 3-6, 8-10), three of which (ca-ses 3-5) revealed positive anti-HBe tests for which the anamnestic response was partially attributed to a previously resolved HBV infection. A further three cases (cases 8-10) revealed negative anti-HBe status but appeared to be classified as truly complete vaccinees according to official vaccination records, their anamnestic responses being partially attributed to a previous vaccination, although, it proved to be impossible to differentiate between a previously resolved HBV infection situation from a false positive anti-HBc for these three cases solely dependent upon their vaccination booster strategy. The case 6 which revealed an anamnestic anti-HBs response had an inconsistent anti-HBc result (anti-HBc status changed from positive in the first sampling process to negative in the follow-up sampling round). For this participant, it would seem likely that his initial positive anti-HBc status was assumed to be a false positive. Although this participant's previous vaccination history was unknown, we concluded that the observed anamnestic anti-HBs response for him was best regarded as resulting from a previous vaccination.

Three subjects revealed no anamnestic response (cases 1, 2 and 7). Case 1 proved to

be anti-HBe po-sitive and HBV DNA positive and case 2 revealed a positive anti-HBe and a negative HBV DNA status. Accordingly, these two cases were putatively defined as carriers with undetectable HBsAg. Further complete vaccination was not required for these two subjects. Case 7, who exhibited negative anti-HBe and negative HBV DNA test results, was invited to receive complete vaccination. This case revealed primary vaccination response. Hence, case 7 was assumed to represent a false positive anti-HBc result.

Discussion

This study confirmed that, 15 years subsequent to a mass hepatitis B vaccination program, the low prevalence of isolated anti-HBc antibody paralleled with the decreasing trends for anti-HBc and HBsAg, this being the first study engaged to explore the significance of anti-HBc alone individuals among a vaccination population.

The seroprevalence of HBsAg among adolescents aged between 12 and 15 years and resident in Taishi Township appeared to be unexpectedly high at 7.1%. By comparison to Hsu et al's report discussing the nation-wide survey of Taiwan, the seroprevalence of HBsAg in our study was higher than was the case for the nation-wide survey of Taiwan for birth cohort born between July 1984 and June 1986 inclusively, i.e., 11.5% (49/425) for group A in our study vs. 6.3 %

(94/1,500) for the study of Hsu et al ($p < 0.001$) 6. In addition, the seroprevalence of HBsAg in Taishi Township among a cohort born between July 1986 and December 1989 inclusively (group B in our

study) also appeared to be greater than for the nation-wide Taiwanese survey (i.e. 4.4 % [31/701] vs. 1.7% [26/1,500], $p < 0.001$) 6. Moreover, Ni et al reported that the rate of HBsAg seropositivity among individuals aged between 13 and 14 years, 15 years subsequent to a mass vaccination program in Taipei City, was only 0.5% 4. In this rural township study that we conducted, the complete vaccination coverage rates during infancy among individuals for a similar birth-year population was lower than was the case for the nation-wide survey (72.4% [312/431] vs. 87.2% [1,308/1,500], $p < 0.001$) 6 and for the Taipei metropolis study (72.4% [312/431] vs. 97% [359/371], $p < 0.001$)   3. According to a seroprevalence survey conducted at the beginning of the nation-wide vaccination program, we found that the [HBV] carrier rate among pregnant woman in Yunlin County (20%) was quite similar to the corresponding figure for the general situation for Taiwan (18%), and even the rate for a metropolis such as Taipei City (18%) 7. The   HBV infection rate among adults prior to the vaccination program in Taishi Township was, quite reasonably, believed to be not outstanding at the time. Therefore, the most likely explanation for a higher HBV infection-rate among adolescents in this township was that the greater rate was

due to a lower vaccination coverage rate for the area.

In various reports worldwide, the prevalence of isolated anti-HBc in different populations has ranged from 0.1% to 20%, dependent upon whether HBV was endemic or not 1,8,10, 11,13-14. Surveys from USA and Europe have revealed that the prevalence of anti-HBc alone was only around one to four percent for wes-tern countries 1. In Taiwan, the prevalence of isolated anti-HBc was about 10-15% among adults before the mass vaccination 8-9, with a corresponding figure of 0.9% among adolescents 15 years subsequent to the nation-wide vaccination program in this study. In addition to the impact of mass vaccination program, the age of these studied subjects (adolescents, but not adult) might also contribute to its lower prevalence of anti-HBc alone. This lower prevalence figure for anti-HBc alone as revealed by our study appears to parallel the corresponding figure for western countries where HBV is not prevalent.

The evaluation of the response to a hepatitis B vaccine booster in order to distinguish whether isolated anti-HBc is related to a prior exposure to HBV is proposed 8,10-11,13-14. The anamnestic anti-HBs response, which meant past HBV infection with a loss of anti-HBs, was reported within a range of 4.2-42.5% among anti-HBc alone subjects. Studies with the result of higher anamnestic anti-HBs response were mostly reported from higher HBV endemic areas   10. Individuals without anamnestic response were further investigated in order to reveal whether there existed an accompanying primary response or not after complete three doses vaccination-program. Anti-HBc in those who had a primary response to complete hepatitis B vaccination were assumed to be a false-positive 10-11, and these individuals comprised the major part (perhaps >70%) of anti-HBc alone for low HBV-prevalent districts 11. By contrast, non-responders to complete vaccination were here considered to be true HBV carriers with undetectable HBsAg by current EIA assays. However, some authors have queried whether the booster response is insufficiently sensitive to predict a previous contact with HBV, because some isolated anti-HBc subjects might demonstrate a history of a previous HBV infection without their revealing a vigorous anti-HBs response 8-9. Hence, the screening of additional HBV markers (anti-HBe or HBV DNA) might be a more effective strategy 8,12,15. The detection of anti-HBe in this circumstance may be useful as predictive evidence suggesting against a false-positive anti-HBc result 12. Accordingly, Chan et al's report conducted in Taiwan for the population prior to a mass vaccination program revealed that most (nearly 75%) anti-HBc alone individuals do exhibit evidence of previous HBV exposure (anti-HBe positive and/or HBV DNA positive) 8. The titer of anti-HBc may provide some assistance in defining the nature of isolated anti-HBc 14,16, although this may not always be the case 8.

We utilized extensive investigation in order to define the meanings of anti-HBc for these ten anti-HBc alone subjects. The putative explanations for the anti-HBc in these ten cases were: five true positive (two HBV carriers, including one low-level viremia, i.e., occult HBV infection; three resolved past HBV infection), and two false positive anti-HBc results. The last three previous vaccinees (cases 8-10) could not be accurately differentiated as true positive as opposed to false positive cases. This proportion of true positive anti-HBc (50%) in this study lay in the range of the level existing in Taiwan prior to the era of the mass vaccination (75.5%, Chan et al) 8 and that le-vel in western countries where HBV were not endemic (<30%) 1,11. Although the universal vaccination program has reduced the size of HBV carrier-pool, such adolescents may still live in an HBV-endemic environment and occasions of subclinical

HBV infection can certainly occur. From this study, it would appear that the universal vaccination program has decreased the prevalence of anti-HBc alone, but it has not changed the nature of anti-HBc alone markedly. This point may render valuable information, and anti-HBc alone individuals among this vaccinated cohort may still harbor the risk for viral transmission.

Several reasons for the lack of HBsAg in anti-HBc alone individuals have been previously presented 1,17. HBsAg may be hidden in a circulating immune complex. HBsAg synthesis may be down-regulated by co-infection with HCV. Mutations in the pre-S or surface antigen itself (especially "a" determinant) may render HBsAg undetectable by conventional EIA methods. Certainly, a proportion of anti-HBc alone subjects may be low-level viremia carriers, with HBsAg concentrations lying below the detection li-mit of current serological assays. Recently-introduced sensitive EIA tests using a novel electron spin technique may overcome this problem 16. Our cases shown no evidence of hepatitis C infection, however, a possible surface gene escape mutation warrants future investigation.

In conclusion, the prevalence of anti-HBc alone was only 0.9% in a hepatitis B vaccinees-cohort 15 years following a mass vaccination program. The nature of anti-HBc in those isolated anti-HBc adolescents were considered to be true positive for 50% of cases. Low-level viremia or occult HBV infection was noted to exist and it appeared theoretically possible for viral transmission to occur.

Acknowledgements

References

1.Grob P, Jilg W, Bornhak H, Gerken G, et al. Serological pattern "anti-HBc alone": report on a workshop. J Med Virol 2000; 62: 450-5.

2.Sung JL, Chen DS, Lai MY, et al. Epidemiological study on hepatitis B virus infection in Taiwan. Chin J Gastroenterol 1984; 1: 1-9

3.Chen HL, Chang MH, Ni YH, et al. Seroepidemiology of hepatitis B virus infection in children. Ten years of mass vaccination in Taiwan. JAMA 1996; 276: 906-8.

4.Ni YH, Chang MH, Huang LM, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. Ann Intern Med 2001; 135: 796-800.

5.Lin DB, Wang HM, Lee YL, Ling UP, Changlai SP, Chen CJ. Immune status in preschool children born after mass hepatitis B vaccination program in Taiwan. Vaccine 1998; 16: 1683-7.

6.Hsu HM, Lu CF, Lee SC, Lin SR, Chen DS. Seroepidemiologic survey for hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization. J Infect Dis 1999; 179: 367-70.

7.Chen DS, Hsu HM, Sung JL, et al. The Hepatitis Steering Committee; The Hepatitis Control Committee. A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers. JAMA 1987; 257: 2597-603.

8.Chan CY, Lee SD, Tsai YT, Lo KJ. Hepatitis B vaccination alone is not adequate for the categorizing of adult subjects with isolated anti-HBc. J Gastroenterol Hepatol 1995; 10: 192-7.

9.Wu JS, Tam KM. Immune response to hepatitis B vaccine subjects positive for serum hepatitis B core antibody alone. J Formosan Med Assocc 1988; 87: 944-7.

10.Ural O, Findik D. The response of isolated anti-HBc positive subjects to recombinant hepatitis B vaccine. J Infect 2001; 43: 187-90.

11.Silva AE, McMahon BJ, Parkinson AJ, Sjogren MH, Hoofnagle JH, Di Bisceglie AM. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. Clin Infect Dis 1998; 26: 895-7.

12.Howell DR, Barbara JA. Isolated antibody to hepatitis B core antigen and the immune response to hepatitis B vaccination. JAMA 1988; 260: 636-7.

13.Lok ASF, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. Hepatology 1988; 8: 766-70.

14.Aoki SK, Finegold D, Kuramoto IK, et al. Significance of antibody to hepatitis B core antigen in blood donors as determined by their serologic response to hepatitis B vaccine. Transfusion 1993; 33: 362-7.

15.Liesnard CA. Hepatitis B vaccination in persons with isolated hepatitis B core antibodies. Clin Infect Dis 1999; 28: 932.

16.Aoki M, Saito T, Watanabe H. Clinical significance of a highly sensitive enzyme immunoassay of hepatitis B surface antigen using a novel electron spin technique. J Med Virol 2002; 66: 166-70.

17.Weber B, Melchior W, Gehrke R, Doerr HW, Berger A, Rabenau H. Hepatitis B virus markers in anti-HBc only positive indivi-duals. J Med Virol 2001; 64: 312-9.

全面 B 型肝炎疫苗接種 15 年後單獨 B 型肝炎核心抗體存在之盛行率與其意義

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摘　　要

台灣在 B 型肝炎全面疫苗接種 15 年後，已大幅降低 B 型肝炎之感染率與帶原率。單獨 B 型肝炎核心抗體存在（即核心抗體陽性、表面抗原陰性、表面抗體陰性）之意義與盛行率在疫苗接種世代則未知。我們以雲林台西國中青少年疫苗接種世代為研究對象，採用檢測 e 抗體、疫苗補接種探究免疫記憶、以實時間定量聚合鍊鎖反應檢測病毒量等多重方式，來決定單獨 B 型肝炎核心抗體存在之意義。該鄉之青少年於嬰兒期之疫苗接種率為 72.4%（312/431），B 型肝炎感染率（核心抗體陽性）與帶原率（表面抗原陽性）分別為 19.5%（219/1,126）與 7.1%（80/1,126）。單獨 B 型肝炎核心抗體存在盛行率為 0.9%（10/1,126）。在這 10 位單獨 B 型肝炎核心抗體存在之青少年，5 位 e 抗體陽性；其中 3 位有免疫記憶，另 2 位無免疫記憶者視為帶原者（1 位血中可偵測到病毒；281 copies/mL）。1 位 e 抗體陰性且無免疫記憶者，接種三劑疫苗後，表面抗體轉陽；故核心抗體推論為假陽性。1 位追蹤核心抗體呈陰轉，故核心抗體亦為假陽性。其餘 3 位單獨 B 型肝炎核心抗體之意義無法確定。單獨 B 型核心抗體存在之盛行率在疫苗接種世代只有 0.9%；有一半的單獨核心抗體存在代表曾受感染，其中 1 位更可以在血中偵測到病毒。

Table 1 Vaccination histories and their seroprevalence for HBV for subjects born after July 1986 (group B)

Vaccination Histories	No. (%)	Anti-HBc No. (%)	HBsAg No. (%)
Known Vaccination History	431 (100%)	51 (11.8) [c]	16 (3.7) [d]
0~2 doses	119 (27.6)	19 (16.0) [a]	7 (5.9) [b]

3~4 doses	312 (72.4)	32 (10.3)[a]	11 (3.2)[b]
Unknown Vaccination History	270	37 (13.7)[c]	15 (5.6)[d]

[a] p = 0.132; [b] p = 0.287; [c] p = 0.484; [d] p = 0.262

Table 2 Seroprevalence for HBV amongst study adolescents

	Total (N = 1,126)	Group A (N = 425)	Group B (N = 701)
No. (%) of anti-HBc Positive Adolescents	219 (19.5)	131 (30.8)[a]	88 (12.6)[a]
No. (%) of HbsAg Positive Adolescents	80 (7.1)	49 (11.5)[b]	31 (4.4)[b]
No. (%) of anti-HBc alone	10 (0.9)	2 (0.5)	8 (1.1)

Group A: subjects born between July 1984 and June 1986 inclusively; Group B: subjects born between July 1986 and December 1989 inclusively, see text.

[a] P < 0.001; [b] P < 0.001

Table 3 Demographics and natures of ten anti-HBc alone study subjects

Case /Sex	Group	Vaccine history	Initial cAb titer [b]	Follow-up cAb titer [b]	eAb	Anamnestic response (sAb titer [c])	Primary response (sAb titer [c])	HBV DNA (Copies/mL)	Interpretation of cAb
1/M	B	NA	0.052	0.067	P	No (0)	ND [a]	P (281)	HBV carrier
2/M	A	NA	0.065	0.059	P	No (0)	ND [a]	N	HBV carrier
3/F	B	NA	0.040	0.063	P	Yes (124.2)		N	Past resolved HBV infection
4/F	B	NA	0.089	0.053	P	Yes (139.6)		N	Past resolved HBV infection
5/F	B	0 dose	0.122	0.127	P	Yes (> 1000)		N	Past resolved HBV infection
6/F	A	NA	0.220	1.608(N)	N	Yes (> 1000)		N	cAb false positive
7/M	B	NA	0.305	0.169	N	No (37)	Yes (340)	N	cAb false

								positive
8/F	B	4 doses	0.088	0.060	N	Yes (92.2)	N	Unknown
9/M	B	3 doses	0.286	0.259	N	Yes (140.8)	N	Unknown
10/M	B	3 doses	0.658	0.463	N	Yes (> 1000)	N	Unknown

P: positive; N: negative; NA: not available; M: male; F: female.

[a] ND: not done due to positive anti-HBe result against a false positive anti-HBc.

[b] Anti-HBc titer is presented as S/CO value; repeated ant-HBc was checked at least three months apart.

[c] Anti-HBs titer is presented as mIU/mL.