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Analysis of Serum Levels of IgA Antibodies to Epstein Barr Virus Capsid Antigens in the Spouses and the Children of Patients with Nasopharyngeal Carcinoma

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OBJECTIVE To analyze the serum levels of IgA antibodies to Epstein Barr virus capsid antigens (EBV/IgA/VCA) in patients with nasopharyngeal carcinoma (NPC) and in their spouses and children in order to further evaluate the risk of developing the disease in family members of NPC patients.
METHODS Four categories of sera were used to detect EBV/IgA/VCA using the immunoenzyme method. In our study 317 biopsy-confirmed NPC patients, 317 spouses and 317 children of the NPC patients, as well as 413 healthy subjects as the controls that came from the same area were enrolled.
RESULTS The positive rate of EBV/IgA/VCA was 97.2%, 14.2%, 19.9% and 3.1% in the NPC patients, the spouse and child groups, and in the control group, respectively. The positive rate was significantly higher in the NPC group than in the other 3 groups, and it was also significantly higher in the spouse and in the child groups than in the control group ($P < 0.001$). The results of the relative to identified distribution unit (Ridit) analysis showed that the average Ridit values were 0.860, 0.404, 0.424 and 0.356 respectively in the NPC patients, in the spouse and child groups, and in the control group. The antibody titer of IgA/VCA was significantly higher in the NPC group than in the other 3 groups, and it was also significantly higher in both the spouse and child groups than in the control group ($P < 0.001$). The OR values of positive EBV/IgA/VCA antibody were 5.09 and 7.63, respectively in the spouse and child groups. No significant differences were found in the positive rates or in the titers of IgA/VCA antibody between the groups of spouses and children ($P > 0.05$).
CONCLUSION Positive detection of EBV/IgA/VCA antibody occurs in familial aggregation, as there is ample opportunity for EBV reactivation in the spouses and in the children of NPC patients. These individuals with a high risk of developing the NPC should be closely followed in order to detect the disease at an early stage.

KEY WORKS: nasopharyngeal carcinoma, Epstein-Barr virus, antibody, family member.

Introduction

Epstein-Barr virus (EBV), environmental and genetic factors are 3 potential etiologic agents of nasopharyngeal carcinoma (NPC), and the relationship between EBV and NPC remains a topic of very active research interest[1]. Results of many studies have confirmed that all NPC patients have very high titers of anti-EBV antibody in their serum, and that the detection of EBV/IgA/VCA antibodies has sig-

nificant value when applied to mass screening and to the diagnosis of NPC[2]. The purpose of our study is to investigate the distribution of the EBV/IgA/VCA antibodies in NPC patients and in their family members, and to provide evidence for the utility of NPC prevention where indicated in the general population.

Materials and Methods

NPC group

A total of 317 NPC patients, from Wuzhou, Guangxi Zhuang Autonomous Region and the surrounding cities and counties of high incidence were randomly selected. The diagnosis of NPC was made by pathologic examination in all of the cases. There were 214 males and 103 females, with the age ranging from 30 to 77 years old.

Spouse group and child group

The spouse group was composed of spouses of the patients who were selected for the NPC group. The age of the spouses ranged from 28 to 75. Children of NPC patients who voluntarily took part in the study were designated the child group. Among subjects of the child group, 213 were male and 104 were female. The age of these subjects ranged from 7 to 48.

Normal control group

After physical health examination, a total of 413 healthy local subjects were randomly selected for the control group, in which 241 were male and 172 female, and with an age range from 19 to 76. EBV-related diseases were ruled out after an examination of the selected subjects.

Detection

An immunoenzymic method for the detection of EBV/IgA/VCA antibody in the sera of the subjects, set up by our laboratory, was applied[3]. Antibody titers ≥ 1:10 were regarded as positive.

Statistical analysis

SPSS 13.0 was applied. Chi-square test was used for the comparison of the intergroup positive rates, for the general comparison of the sizes of the test ($\alpha = 0.05$), and for the multiple comparison ($\alpha' = 0.0083$). Ridit analysis was conducted for comparison of the distributions of intergroup antibody titers. All 4 groups were combined and were regarded as the standard group, and the size of test was $\alpha = 0.05$.

Results

The distributions of the EBV/IgA/VCA antibody in the serum of each group are shown in Table 1. There were significant differences in the comparison of the positive rates of the antibody in the 4 groups, $\chi^2 = 851.8$, $P = 0.000$. In the multiple comparison of the sizes of the test, comparisons were made between the NPC and the control groups, the spouse and the control groups, and the child and the control groups, and statistically significant differences were present ($\chi^2 = 643.4$, 29.9 and 53.8, $P = 0.000$, 0.000 and 0.000, respectively). There were no significant differences in the comparison between the spouse group and the child group ($\chi^2 = 3.6$, $P = 0.057$).

The OR (odds ratio) of the positive infection rate of EBV/IgA/VCA was 5.09 (95%CI: 2.70-9.62) and 7.63 (95%CI: 4.12-14.15), respectively in the spouse and child groups.

Regarding the comparison of distributions of antibody titers, the average Ridit values were 0.860 (95%CI: 0.847-0.874), 0.404 (95%CI: 0.387-0.421), 0.424 (95%CI: 0.405-0.442) and 0.356 (95%CI: 0.349-0.363), respectively in the NPC, the spouse, the child and the control groups. Further, there was a significant difference in the general comparison between the groups ($F = 1108.7$, $P = 0.000$), among which the NPC group had a significant difference in respective comparison with the other 3 groups, $P = 0.000$. There was no significant difference in comparison between the spouse group and the child group ($P = 0.055$), and there were significant differences in the respective comparison between the control group and the spouse group, and between the control group and child group, $P = 0.000$. The 95%CI of average Ridit values in the antibodies of the 4 groups is demonstrated in Fig.1.

Table 1. Distribution of EBV/IgA/VCA antibodies in the serum of each group.

Group	*n*	No. of cases with IgA/VCA antibody titer (≥ 1:10)							Positives (%)
		Negative	10	20	40	80	160	320	640	
NPC	317	9	51	33	71	68	49	25	11	308 (97.2)
Spouse	317	272	28	11	5	0	1	0	0	45 (14.2)
Child	317	254	56	5	1	1	0	0	0	63 (19.9)
Control	413	400	11	1	1	0	0	0	0	13 (3.1)

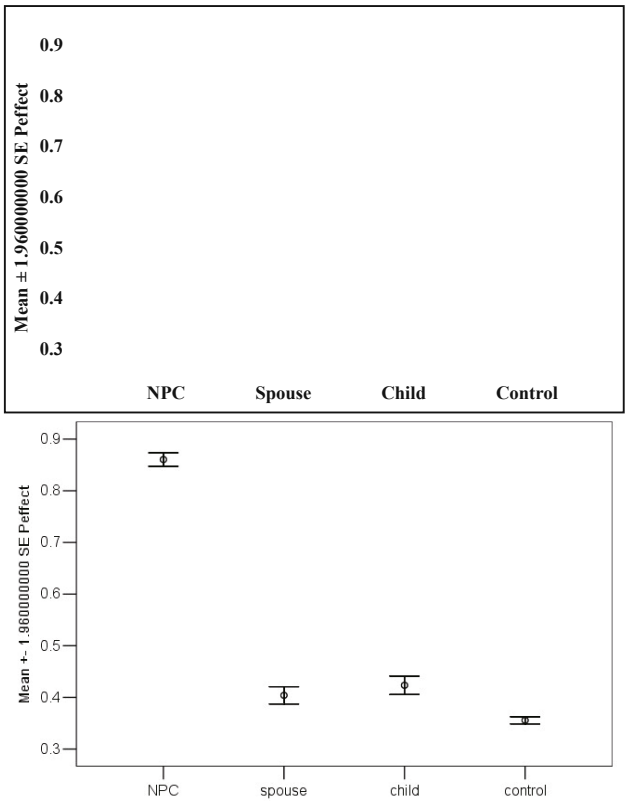

Fig.1. 95%CI of average Ridit values in the EBV/VCA-IgA antibody titer of each group.

Discussion

Nasopharyngeal carcinoma (NPC) is usually found in the Asian population, and the incidence rate of the disease is high in many regions of China, such as Guangdong, Guangxi, Hunan and Fujian, etc., with an apparent characteristic endemic distribution. Three etiologic factors, which might be related to the onset of NPC, were established in our previous research, i.e., EBV infection, genetic characteristics, and environmental carcinogenic agents[4]. The biological foundation of a genetic predisposition to NPC suggests that the primary aberrant chromosomal manifestations of NPC are as follows: compared with those in the control group the incidence of abnormal chromosomes, the increase in chromosome fragility and the rate of spontaneous sister chromatid exchange (SCE) are higher in all 3 study groups, i.e. the NPC patient, the spouse and the child groups. Moreover, the effect of the viral chromosome is obvious thus the rate of SCE is even higher in cases with positive IgA/VCA antibody[5]. It is believed that EBV has a close temporal relation to the onset of NPC, and that VCA is the product of EBV lytic infection. The expression of IgA/VCA can be regarded as a marker predicting the progression of NPC and as a clue for the reactivation of EBV replicating at the mucous membrane surface[6]. Our results indicate a positive rate of EBV/IgA/VCA antibody in NPC patients of 97.2%, which was similar to that in the previous reports[7]. The positive rate and the average level of antibody were significantly higher in the NPC group than in the other 3 groups ($P < 0.001$), which shows that IgA/VCA antibodies can be used as a serological marker in the diagnosis of NPC.

After our case-control study, it was found using univariate logistic analysis that the risk of developing NPC in subjects with positive EBV/IgA/VCA antibodies and with a family history of NPC is increased 2.9 times. Further, both the univariate and multivariate logistic analysis showed that there is a 3-fold or greater risk of developing NPC in the first degree relatives of an NPC patient. There is an even higher potential risk of developing NPC in the first degree relative of an NPC patient from a high-risk area, who is also EBV/IgA/VCA antibody positive[8]. Latent EBV in patients will frequently be reactivated if a certain level of EBV/IgA/VCA antibody in blood exists continuously. During repeated reactivation, EBV may easily bring about genovariation, and thus play a role in the formation of NPC. In our study, the positive rates of IgA/VCA antibody were 14.20% and 19.87% respectively in the spouses and children of the NPC patients, which are significantly higher than that of 3.15% in the normal control group ($P < 0.001$). At the same time, the average levels of the antibody were significantly higher in the spouse and the child groups than in the control group ($P < 0.001$). Compared with the control group, the infection risk associated with EBV/IgA/VCA antibody positivity was 5.09 and 7.63 times higher than that in the spouse and children of NPC patients. However, no significant differences in the positive rate and level of the IgA/VCA antibody between the spouse group and the child group were found. This indicates that the detection of EBV/IgA/VCA antibody positive has a familial aggregation, and that the opportunity of the EBV reactivation is higher in the family members of NPC patients than that in the normal subjects, which might associated with a common living environment and eating habits. The risk of EBV reactivation may be relatively higher in the child group compared to the other groups, and related research is now underway in order to make it clear if the risk is correlative to genetic factors.

The inherent individual and hereditary susceptibilities to EBV play a key part in the onset of NPC. Ninety per cent of the population is infected with EBV by the age of 2, however, in general, serum levels of EBV antibody remain low since the virus has typically not been activated[9]. It has been reported that the risk of invasive NPC is 12 times higher in the population with EBV reactivation than in those without a previous reactivation or re-infection[10]. Studies have also shown that NPC can be found 1 or even 10 years after the detection of EBV/IgA/VCA antibodies. During the period of the positive detection, antibody levels were increased with the progression of the NPC until the patients became symptomatic and the disease was finally found[2,11]. Based on the results of our study, the positive rate and

the antibody level of IgA/VCA in the serum are both higher in family members of NPC patients than in those in the normal control group, which indicates that the risk of developing NPC is higher in this population than in normal subjects. Therefore, it is necessary that an EBV serologic examination be conducted from time to time in the population of patients with a family history of NPC and that development of the EBV/IgA/VCA antibody in the serum be closely monitored in order to find the NPC as early as possible.

References

1 Cen XT, Wei L, Wu WH, et al. Research of nasopharyngeal carcinoma in HK University Medical School over recent 10 years. Zhongguo Zhongliu Linchuang 1997; 24: 645-650 (Chinese).
2 Deng H, Zeng Y, Liang JP, et al. The basic screening project in 488 683 persons for nasopharyneal carcinoma. Zhongliu 2005; 25: 152-154 (Chinese).
3 Cheng JR, Pi ZM, Mo YK, et al. Serological screening of nasopharyngeal carcinoma in part of the workers from Wuzhou city. Linchuang Zhongliuxue Zazhi 1997; 2: 46-48 (Chinese).
4 Dong ZW. Development of cancer research in China. Beijing: Peking University Medical Press 2007; 389-400 (Chinese).
5 Shang XL, Xie ZQ, Huang ZB. Risk factor of nasopharyngeal carcinoma. Xiandai Yufang Yixue 2008; 35: 206- 207 (Chinese).
6 Raab-Traub N. Epstein-Barr virus in the pathogenesis of NPC. Semin Cancer Biol 2002; 12: 431-441.
7 Cheng JR, Pi Zm, Mo YS, et al. Analysis of EBV/IgA/VCA antibody with clinical manifestations of nasopharyngeal carcinoma. Linchuang Zhongliuxue Zazhi 1998; 3: 31-32 (Chinese).