HLA gene and clinical study of insulin dependent diabetes mellitus (IDDM) in Chinese individuals

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The prevalence rate of diabetes in China was 0.67% in 1980. For the last ten years, the prevalence rate has increased 0.1% every year. The total number of diabetics in China is enormous, in the range of 12-15 million people; 10% have insulin dependent diabetes (IDDM) and 90% have non insulin dependent diabetes (NIDDM).

1) HLA Typing DR3 was statistically increased in Chinese IDDM patients; relative risk 7.89, Fisher's p 5.91 x 10^{-6} corrected p 4.14 x 10^{-6}. DR3 is increased in most Caucasians and American Blacks, but not in Japanese individuals.

2) HLA-DQA1 and B1 alleles contribute to susceptibility to IDDM IDDM is strongly associated with the presence of arginine in position 52 of the DQ α chain and absence of aspartic acid in position 57 of the DQ β chain in Caucasians. To confirm this association in Chinese, extensive oligonucleotide dot blot hybridisation of PCR-amplified DQA1 and DQB1 genes were studied using samples from 48 IDDM patients and 46 healthy non diabetic control subjects. DQ α 52-Arg and DQ β 57-non-Asp are strongly associated with IDDM susceptibility as compared with controls ($p < 0.001$ and 0.006, respectively). DQ β 57-non-Asp homozygosity is associated with increased susceptibility to IDDM. DQ β 57-Asp homozygosity is associated with protection against IDDM; 14.6% of IDDM patients were homozygous for DQ β-Asp, compared with 0% of American patients; 22.9% of IDDM patients were homozygous for DQ β 57-nonAsp, compared with 96% of American diabetic subjects in a previous study. These results suggest that the effect of the DQ β 57-Asp variation on Chinese IDDM susceptibility is not as remarkable as in Caucasians, and there may be other alleles which contribute to IDDM susceptibility in Chinese individuals.

3) Familial Aggregation and HLA Typing of Pedigrees in IDDM In 280 cases with IDDM positive family histories of diabetes have been found to be present in 26.8% of IDDM probands. The prevalence of diabetes in relatives has been shown to be 68% in first degree relatives, 28% in second degree relatives and 4% in the third degree relatives. HLA data support the hypothesis that IDDM is a multigenic hereditary disorder.

4). Clinical Features of Microvascular Complications in Long Term IDDM One hundred sixty three individuals with IDDM of more than 10 years in duration were followed. Most complications were microvascular, such as proliferative retinopathy (39/163, 23.9%) and nephropathy (19/163, 11.7%).

We have found that the development and degree of microvascular complications depend on the age of onset, diabetes duration and the long term glycaemic control. Especially, microvascular complications were found to be significantly influenced by glycaemic control in the first ten years after onset.

Introduction

The prevalence of diabetes in China was 0.67% based on our survey in 1980. In the last ten years, it increased gradually at the approximate rate of 0.1% yearly. Due to the population, the absolute number of patients is large.

In China, there are approximately 12-15 million diabetics, and, among them, about 90% are of type II or non-insulin dependent diabetes mellitus (NIDDM); and the other 10% are of type I or insulin dependent diabetes mellitus (IDDM) .

HLA typing

The frequency analysis in HLA of IDDM has been done, especially in HLA-DR. The frequency of DR3 among the IDDM group was very high, reaching 54.84%, but was only 12-13% in the control and NIDDM groups. Obviously, DR3 is increased in IDDM, and its relative risk is 7.89. There appears to be no interrelationship of HLA frequency in the two types of diabetes. Contrary to the Caucasians, DR4 in the IDDM group is not very high in Chinese.

HLA-DQ gene frequency in IDDM

Blood samples were collected from 48 IDDM patients and 46 healthy controls. The dot blot hybridisation test was carried out by using 23 synthetic oligonucleotide probes, among which were 9 for DQ A1 and 14 for DQ B1. The results showed that the distribution of DQ A1 0301 allele was much higher in patients with IDDM than in the controls. According to the 14 nucleotide probes, DQ B1 0601 is much higher in the controls than in the IDDM. However, the 0201 and 0302 alleles are much higher in the IDDM group when compared to controls. DQ A1 0301 shows that arginine is encoded in position 52 of the chain. DQ B1 0201 and 0302 show that alanine is encoded in position 57 rather than aspartic acid. The DQ B1 0601 encoded aspartic acid is in position 57. The results have also shown that there is evidence of increasing frequency of encoded arginine in position 52 of DQ A1 and alanine in DQ B 1 in position 57 in IDDM patients. Controls show a higher frequency of aspartic acid encoded in position 57 of DQ B1. The DQ B1 encoded aspartic acid has a certain protective effect for the patients.

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There was a remarkable difference of the homozygous state of DQ B1 of aspartic acid in position B57 and DQ B1 non-aspartic acid in position 57 between the IDDM group and controls. The homozygous DQ B1 having aspartic acid in position 57 has evidently a higher carrier frequency when compared to the IDDM group ($p<0.01$). The DQ B57 non-aspartic acid homozygous was 22.9% in the IDDM group, while the rate was only 2.2% in the control group. In other words, non-aspartic acid homozygosity results in a higher rate in IDDM patients than in the control group. It shows that when the DQ B1 encoded in position 57 was not aspartic acid, it has a greater chance to result in IDDM.

Comparing these results to the survey from the state of Pennsylvania in the USA, the DQ B1 non-aspartic acid homozygous was only 23% in Chinese, but it was shown that 96% of Americans have that constitution. The ratio of the aspartic acid homozygous state and the occurrence of IDDM is zero in Americans. In Chinese, however, there is still a 15% probability of developing IDDM. This suggests that the protective effect of aspartic acid in position B57 in DQ B1 in Chinese is less effective when compared to Caucasians. The 20 fold difference in IDDM incidence between these two groups seems to be related to the low prevalence of the non-Asp-57 marker in the Chinese control group.

Familial aggregation in IDDM

We have long term follow-up on 280 IDDM patients. Among them, 75 were found to have a positive family history; a rate of 26.8% in our study. This is much higher than in Caucasians, where the rate is only about 10%. This shows that it is very important to pursue long term follow-up with IDDM patients. Our hospital has a life-time follow-up program, and the 75 probands, as mentioned above, have 98 relatives suffering from diabetes about 10-20 years after their own onset of disease. Among those diabetic patients, the occurrence rate of the first, second, and third degree relatives are 68%, 28%, and 4%, respectively.

The HLA typing of 87 members in 13 pedigrees with IDDM has been performed. In the first example, there are exactly the same two haploid types of HLA among the proband and siblings, such as F1, 2, 4, 5, 6, etc. in a total of 9 families. However, not always do all the siblings have the disease. In the second example, although there is only one haploid common to the probands, all the siblings may contract diabetes, such as family 10. In the third example, the proband's parents, father, or mother, who also carried HLA DR3 or DR4, presented clinically as a NIDDM, such as F11 and F13. Those examples tell us that IDDM is a multigenic hereditary disease. As to the cause of the diabetes, environmental factors are very important, and they are superimposed on the inheritance factor and do not always result in clinical disease, even with the same haploid type as the individuals.

Clinical features of microvascular complications in long term IDDM

The microvascular complications have been studied in a total of 163 patients for a duration of over 10 years. Among them are 62 males and 101 females; the average age of onset of the disease was 18 years, and the average duration was 20 years. For those whose duration period was between 10-20 years, the rate of proliferative retinopathy and nephropathy were 15.4% and 4.4%, respectively, but for those with a duration of over 20 years, it increased to 34.7% and 20.8%, respectively. This shows that the prevalence of those complications of IDDM is related to the duration of the diabetes. Patients at the age of 10-19 years get the most IDDM complications, which is significantly higher than the patients who are 20 or more. This is probably due to the difference in the ability to control plasma glucose level between the two age groups.

We have also studied the relationship between the complications of IDDM and the degree of glycaemic control. The glycaemiic control was divided into three degrees based on the effect of control of plasma glucose during the first decade after the onset of IDDM: the first degree was the best (relatively normal plasma glucose level); second degree had a slightly higher plasma glucose level; and third degree was not well controlled. The patients of the third degree group often presented with symptoms like diabetic ketoacidosis, high level of plasma glucose, and complications like proliferative retinopathy and nephropathy reaching 76% and 50%, respectively. In contrast to the former group, neither retinopathy or nephropathy was found in the first degree group. This shows that the quality of the plasma glucose control within the first ten years directly affects the occurrence of complications.

In order to evaluate the quality of control and its impact on the outcome of the disease, patients with IDDM were divided into two groups: either continued or non-continued treatment. The continued treatment group had 60 patients who had long term follow-up treatment without interval over more than 3 years during the first 10 years after onset as an outpatient. The other group (non-continued treatment) had 103 patients who did not follow-up the interval at least over 3 years during the first 10 year period. About 90% of patients in the continued treatment group had glycaemia control classified as first degree. In the non-continued treatment group, approximately 80% of patients were either second or third degree of glucose control. When comparing groups, it is obvious that the continued treatment group showed lower complications than the non-treatment group.

Conclusion

There are 20 patients who did not present with either proliferative retinopathy or nephropathy at over 20 years of follow-up treatment as an outpatient. This raises the following questions, what should we do for outpatients? The following are some important guidelines:

1) to educate: knowledge of diabetes,

2) to make appointments to check the plasma glucose, haemoglobin A1, etc. during each visit,

3) to instruct on self-injection of insulin and self-reporting techniques,

4) to adjust to an interventionary diet and dosage of insulin,

5) regular fundoscopic examination and check of urine albumin excreta rate (AER).

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中國胰島素依賴型糖尿病的 HLA 基因及臨床研究

摘要

1980 年，中國糖尿病的患病率爲 0.67%。近 10 年來，患病率每年增高 0.1%。糖尿病病人約爲 一千二百萬至一千五百萬，10% 爲胰島素依賴型，90% 爲非胰島素依賴型。

1. HLA 分型：胰島素依賴型糖尿病人 HLA-DR3 抗原頻率顯著增加，相對危險率 7.89，校正 P 值爲 4.14×10^{-4}。DR3 在歐洲人群及美國黑人中是增高的。日本的研究無明顯增高。

2. HLA-DQA1 及 B1 等位基因與胰島素依賴型糖尿病易感性相關：DQ α 52-精氨酸及 DQ β 57-非天門冬氨酸與胰島素依賴型糖尿病高度相關已在歐美研究中証實，我們在 48 例病人及 46 名健康人中進行 DQA1 及 B1 等位基因研究，發現與歐美報告相似結果。DQ β 57-天門冬氨酸純合子具有保護作用，胰島素依賴型糖尿病人中有 14.6% 是 DQ β 57-天門冬氨酸純合子，22.9% 是非天門冬氨酸純合子（美國報告分別爲 0% 及96%），因此 DQ β 57-天門冬氨酸的變化對我國胰島素依賴型糖尿病易感性的影響不如白種人顯著。

3. 家族聚集及家系 HLA 分型：280 例病人中 26.8% 有糖尿病家族史，68% 爲一級親屬，28% 爲二級親屬，1% 爲三級親屬，HLA 分型的家系研究表明胰島素依賴型糖尿病是多基因遺傳性疾病。

4. 微血管併發病：163 例病程超過 10 年的胰島素依賴型糖尿病，24% 有增殖性視網膜病變，12% 有糖尿病腎病。微血管併發病的發生與糖尿病發病後第一個 10 年的血管控制程度密切相關。