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Familial Case of Type 1 Diabetes Mellitus (T1DM) with Similar Onset and HLA Analysis

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Abstract

Subjects: Cases are two patients with type 1 diabetes mellitus (T1DM), with the characteristic relationship and onset situation. Case 1 is 46-year-old daughter and case 2 is 69-year-old mother. They have been living apart and they rarely meet together. Twenty-two months after the onset of T1DM case 1, case 2 also developed T1DM. They did not notice clinical manifestation of upper respiratory infection, or they did not have any stressful matters before the onset of T1DM.

Results: Their data in case 1 *vs* 2 were as follows: BMI 21.3 *vs* 19.8, HbA1c 10.3% *vs* 9.8%, anti-IA-2 antibody (IA-2 Ab) 2.1 *vs* 6.0 (<0.4), anti-GAD antibody (GAD Ab) 24 *vs* 10000 (<1.5), HLA-DR type DR9 / DR13 *vs* DR4/DR13.

Discussion and conclusion: These 2 cases have characteristic mode for the onset of T1DM. In Japanese race, DR4 and DR9 have rather high sensitivity for T1DM, DR15 (DR2) has resistance for T1DM and DR13 has unremarkable influence. From these, HLA-DR type would be possible involved in the onset of T1DM, and further investigation would be expected.

Keywords: Type 1 diabetes mellitus (T1DM), Anti-IA-2 antibody, Anti-GAD antibody, HLA-DR type.

Abbreviations: Type 1 Diabetes Mellitus (T1DM); Tyrosine Phosphatase-related Islet Antigen 2 (IA-2 Ab), Anti-glutamic Acid Decarboxylase Antibody (GAD Ab), Human Leukocyte Antigen (HLA).

Introduction

In Type 1 diabetes mellitus (T1DM) has been one of the common autoimmune disorders. Its pathophysiological mechanism is the immunological destruction of the β cells of the pancreas. It will cause the dysregulation of glucose variability and metabolism. T1DM has reported having family cluster associated with an overall genetic risk [1-3].

Furthermore, the association analysis of HLA loci has shown the presence of T1DM susceptibility [4]. In order to proceed with the research of T1DM genes, an international collaboration this is the Type 1 Diabetes Genetics Consortium, has continued to evaluate lots of T1DM families from various countries [5]. For related predisposition of T1DM, there were some findings that combination of HLAA24, -DQA1*03, and -DR9 could contribute to the acute-onset and early destruction in the

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β cells of the pancreas, and that HLA-DR2 has a protective effect in contrast [6].

Moreover, susceptible, neutral, and protective DR-DQ haplotypes for T1DM risk have been identified in the analyses of Caucasian and Asian families [7]. The most susceptible haplotypes are the DRB1*0301-DQA1*0501-DQB1*0201 and the DRB1*0405-DQA1*0301-DQB1*0302, DRB1*0401-DQA1*0301-DQB*0302, and DRB1*0402-DQA1*0301-DQB1*0302 haplotypes. Thus, DR4 has been frequently involved in the risk.

As related matters with mentioned above, we have experienced two cases of acute onset of T1DM which are daughter and mother. These clinically impressive cases are presented in this report.

Case presentation

Case 1 is 46-year-old female who has been working in regular daily life, without any remarkable disease or health problem in the past. She developed acute symptoms of general malaise and weight reduction for 5 kg. She was diagnosed to have diabetes in another clinic, and was transferred to our clinic for further evaluation and treatment of diabetes.

As basal data, her physical was normal, such as vitals, heart, lung, abdomen and neurological findings. Her Body Mass Index (BMI) was 21.3 kg/m^2. Laboratory examination on routine revealed as follows: HbA1c 10.3%, glucose 277 mg/dL, Hb 12.9 g/dL, WBC 5100/μL, Plt 19.5 × 10 V/μL, AST 16 IU/mL, ALT 18 IU/mL, r-GT 15 IU/mL, TP 6.7 mg/dL, BUN 19 mg/dL, Cre 0.5 mg/dL, Uric Acid 3.2 mg/dL, HDL 82 mg/dL, LDL 95 mg/dL, TG 37 mg/dL. Blood C-peptide <0.1 ng/mL, CRP 0.0 mg/dL.

For adequate diabetic treatment of T1DM, she was started insulin therapy, using short-acting and long-acting insulin. It was successfully performed and several months later HbA1c was maintained 7.2-7.5%.

Case 2 is the mother of case 1. She is 69-year-old female who has not to have any positive previous medical history or family history. She has been staying at home in regular daily life without any remarkable health problems. She has not worked in a certain company, but just continued growing some crops in her home vegetable garden for 2-3 hours a day. About 22 months after case 1 became diabetic, she developed rather acute weight reduction. She was diagnosed to have T1DM. She visited our diabetic clinic and was given further evaluation and treatment for diabetes.

As basal data, her physicals showed unremarkable changes such as vitals, heart, lung, abdomen and neurological findings. Her body mass index (BMI) was 19.8 kg/m^2. Laboratory examination on routine revealed as follows: HbA1c 9.8%, glucose 386 mg/dL, Hb 13.3 g/dL, WBC 5200 /μL, Plt 17.4 × 10 V/μL, AST 22 IU/mL, ALT 21 IU/mL, r-GT 17 IU/mL, TP 7.7 mg/dL, BUN 14 mg/dL, Cre 0.6 mg/dL, Uric Acid 3.3 mg/dL, HDL 68 mg/dL, LDL 99 mg/dL, TG 67 mg/dL. Blood C-peptide <0.1 ng/mL, CRP 0.2 mg/dL, CEA 3.4 ng/mL, TSH 0.4 μU/mL, free T4 1.12 ng/mL.

For her generalized condition as T1DM, she was started to have insulin therapy, including two times of 30 R insulin injections a day. The clinical course revealed efficacy for insulin therapy, and several months later HbA1c was maintained 6.5%-6.8%.

The comparison of the data obtained from case 1 and 2 was summarized in Table 1. It showed the differences in the value of antibodies and the type of HLA-DR.

Discussion

In this report, two cases are clinically rare and meaningful. Case 1 and 2 were daughter and mother with 46 and 69 years old, who had the onset of T1DM in 22 months apart. They do not live together and rarely meet, and neither have any prodromal symptoms such as upper respiratory infection before the onset. There are no exposures or special episodes suggestive of stress to the mind and body. As described above, they were unlikely to have common causes for the onset.

Originally, the relationship between genetic factors and environmental factors has been pointed out with regard to the onset of disease. The environmental factors have usually influenced by 95% and genetic factors are 5%, in ordinary diseases [2]. In these two cases, it seems that there are no common items in environmental factors, with the possible involvement of the genetic factors.

Candidate genes reported to be associated with T1DM include Human Leukocyte Antigen (HLA), Insulin (INS), Protein Tyrosine Phosphatase Non-receptor Type 22 (PTPN 22), and Small Ubiquitin-like Modifier (SUMO). Among them, HLA has polymorphisms of DR and DQ, and it is said that human locus is involved in locus IDDM1 on chromosome 6p21 [1].

Several reports on the relationship between T1DM and HLA were found. Generally, in the case of T1DM in Japanese, data showed susceptible to DR4, DR9, resistant to DR15 (DR2), and unremarkable effect on DR 13 [6].

There has been familial clustering of T1DM, in which about 40-50% of them are involved in the influence of allelic variation in the HLA region [8]. Other studies showed that specific alleles at the DRB1, DQA1, and DQB1 loci are strongly responsible for T1DM [9].

Table 1: comparison of case 1 and 2.

		Case 1	Case 2
Case	Age/sex Relation BMI	46 F Daughter 21.3	69 F Mother 19.8
Diabetes	Blood glucose (mg/dL) HbA1c on first visit (%) Blood C-peptide (ng/mL)	277 10.3 <0.1	386 9.8 <0.1
Antibody	Anti-IA-2 antibody (U/mL) (<0.4) Anti-GAD antibody (<1.5) Thyroid peroxidase antibody (<100) Thyroglobulin antibody (<100)	2.1 6130→24 <100 <100	6.0→1.9 14000 → 10000 <100 1600
HLA-DR	HLA type 1 HLA type 2 Allele 1 Allele 2	DR9 DR13 DRB1*09 DRB1*13	DR4 DR13 DRB1*04 DRB1*13

Concerning Asian-specific HLA haplotypes on susceptibility to T1DM, Japanese and Korean patients were studied [10]. The results were that DRB1*0405-DQB1*0401 and DRB1*0901-DQB1*0303 were confirmed to be two major susceptible HLA haplotypes in the Japanese population [10].

According to the analysis of the HLA-DR and DQ haplotypes in Japanese adult-onset T1DM [11]. There were two major susceptible HLA haplotypes, which were DRB1*0405-DQB1*0401 (DR4) and DRB1*0901-DQB1*0303 (DR9). They were significantly increased in the acute-onset type 1 diabetic patients (AO) and childhood-onset type 1 diabetes (CO) groups, but only DR9 was increased in the slowly progressive type 1 diabetic patients (SO) group [11].

After that, serological subtypes were determined in 3 groups [12]. They are i) normal subjects, ii) typical autoimmune T1DM, and iii) fulminant T1DM which characterized by acute onset and an absence of islet-related auto antibodies, account for 20% of T1DM in Japan. As the result, ii) DR9 but not DR4 was more frequent and DR2 was extremely rare, iii) DR4, but not DR9, was significantly more frequent, while DR1, DR2, DR5 and DR8 were significantly lower than controls [12]. From these, susceptibility and resistance of the HLA subtype to T1DM are distinct between ii) and iii).

In the case of Finland study, there was the study of HLA genes predisposing effect of T1DM [13,14]. The result was that The DRB1*0401-DQB1*0302 haplotype was the most prevalent disease susceptibility haplotype in the Finnish [13,14]. Thus, DRB1*0401 has been involved in the T1DM in Japan and also European country.

Conclusion

In this report, 2 familial cases of T1DM whose onset were 46 and 69 years old with similar clinical manifestation. HLA analyses showed that they have DR 4 and DR 9, suggesting these would be two major susceptible HLA to influence the onset of T1DM in Japan. Further evaluation would be expected for clarification of detail involvement mechanism in future research.

Supplement

This research was conducted in compliance with the ethical principles of the Declaration of Helsinki. Moreover, it was conducted with Japan's Act on the Protection of Personal Information along with the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug (Ordinance of Ministry of Health and Welfare No. 28 of March 27, 1997). We established the ethical committee and meeting was held including physicians, nurse, pharmacist and academic experts. Informed consent and written consent were obtained from the subjects.

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