Arch Clin Med Case Rep 2020; 4 (4): 699-706 *DOI: 10.26502/acmcr.96550253*

Case Report

Japanese Adult-Onset Type 1 Diabetic Sisters with Different Disease States: A Case Report

Koshi Kusumoto[1,2], Nobuyuki Koriyama[1], Nami Kojima[1,2], Maki Ikeda[1,2] and Yoshihiko Nishio[2]

[1]Department of Diabetes and Endocrine Medicine, National Hospital Organization Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima 892-0853, Japan

[2]Department of Diabetes and Endocrine Medicine, Kagoshima University Graduate School of Medical and Dental Science, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan

[*]**Corresponding Author:** Dr. Nobuyuki Koriyama, Department of Diabetes and Endocrine Medicine, National Hospital Organization Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima 892-0853, Japan, Tel: +81-99-223-1151; Fax: +81-99-226-9246; E-mail: koriyama.nobuyuki.wm@mail.hosp.go.jp

Received: 14 June 2020; **Accepted:** 01 July 2020; **Published:** 15 July 2020

Abstract

We encountered type 1 diabetic sisters with different islet-associated antibodies and pancreatic β-cell injury rates. The younger sister had different disease susceptibility human leukocyte antigen (HLA) haplotypes (DRB1*0901-DQB1*0303/DRB1*0802-DQB1*0302) on both chromosomes, while the older sister showed a disease susceptibility HLA haplotype (DRB1*0901-DQB1*0303/-) on one chromosome. Furthermore, the younger sister was positive for anti-glutamic acid decarboxylase antibody (GADA), anti-insulinoma-associated protein-2 antibody (IA-2A), and zinc transporter 8 antibody (ZnT8A), and showed depleted endogenous insulin secretory ability at the time of diagnosis. On the other hand, the older sister was positive only for GADA and ZnT8A, and the ability to secrete endogenous insulin was relatively retained at onset. From our cases and existing reports, we verified that: 1) having a HLA haplotype for disease susceptibility on both chromosomes; 2) having HLA-DQ8 and HLA-A24, -DQA1*03 and -DR9; 3) having more islet autoantibodies including IA-2A and ZnT8A may be involved in accelerating the progression of type 1 diabetes by enhancing the damage to pancreatic β-cells.

Keywords: Type 1 diabetes mellitus; Human leukocyte antigen; Anti-glutamic acid decarboxylase antibody; Anti-insulinoma-associated antigen 2 antibody; Autoantibody to zinc transporter-8

1. Case Report

Type 1 diabetes is caused by a pancreatic β cell-specific mechanism of autoimmune destruction based on the actions of both genetic factors constructed by multiple candidate genes (disease susceptibility genes) and environmental factors [1]. This multifactorial disease usually leads to absolute insulin deficiency [2]. The disease susceptibility gene most strongly involved in type 1 diabetes has been shown to be human leukocyte antigen (HLA) [3]. HLA has class I molecules resulting from A, B and C genes, which mainly present as endogenous antigens to cytotoxic T cells and function as restraining factors in the final stage of immune response, and class Ⅱ molecules resulting from DR, DQ and DP genes, which mainly present foreign antigens to helper T cells and function as restraining factors in the initiation stage of immune response. In particular, class II DR and DQ genes are strongly associated with type 1 diabetes, and DR4 and DR9 are important in serological typing. Haplotypes DRB1* 0405-DQB1* 0401, DRB1* 0802-DQB1* 0302 and DRB1* 0901-DQB1* 0303 in DNA typing have been reported as disease susceptibility types in Japanese populations [4].

On the other hand, the prevalence of siblings among Japanese individuals with type 1 diabetes is reportedly 1–4%, clearly higher than the prevalence of type 1 diabetes in the general population (0.01–0.02%) [5]. This pathology has thus been shown to accumulate in families, but case reports related to this issue remain rare [6-8]. Here, we encountered Japanese type 1 diabetic sisters with different islet-associated antibodies and pancreatic β-cell injury rates. Focusing on the relationship between HLA and islet autoantibodies, we compared and verified the pathological conditions based on existing reports.

2. Case Report

The younger sister became aware of thirst, polydipsia, and polyuria at 24 years old, with an associated weight loss of 4 kg/month. She had a preceding history of drinking a large amount of soft drink. She visited a family doctor, where hyperglycemia was confirmed (hemoglobin (Hb)A1c, 14.3%). No ketoacidosis was observed. No contributory medical or family history was elicited, and there was no history of obesity. She lived with her mother, her sister, her sister's husband and their daughter. Height was 152.6 cm, weight was 54.2 kg, body mass index (BMI) was 23.3 kg/m^2, blood pressure was 109/61 mmHg and heart rate was 75 beats/min. No other physical abnormalities or complications were identified. Fasting blood C-peptide immunoreactivity (CPR) was 0.15 ng/mL, CPR index (CPI) was 0.2, and 24-h urinary (24-h UCPR) was 22 μg/day at the time of onset, revealing that endogenous insulin secretory capacity was almost depleted (Table 1). Islet autoantibody titers were 791.6 U/mL for anti-glutamic acid decarboxylase antibody (GADA), 6.2 U/mL for anti-insulinoma-associated protein-2 antibody (IA-2A), and 406 U/mL for zinc transporter 8 antibody (ZnT8A), and negative results were obtained for islet cell antibody (ICA) (Table 1). Regarding thyroid-related antibodies, anti-thyroglobulin antibody (TgA) showed a normal value of 19 U/mL and anti-thyroperoxidase antibody (TPOA) showed a slightly high value of 17 U/mL (Table 1). HLA displayed A24 and both disease-susceptible haplotypes DRB1* 0901-DQB1* 0303 and DRB1* 0802-DQB1* 0302 (Table 2) [4]. The patient was treated with 24 units/day of insulin aspart and 14 units/day of glargine U300.

At 29 years old (2 years after the onset of the younger sister), the older sister became aware of thirst and malaise, accompanied by weight loss of 5 kg/month. She visited a family doctor, who confirmed hyperglycemia (HbA1c, 9.6%). No ketoacidosis was observed. At the same time, vulvar and vaginal candidiasis was identified. The patient had a history of obesity (up to 81 kg at 24 years old) and had given birth by Caesarean section, although the baby was not abnormally large. She smoked 10 cigarettes/day. Height was 161.5 cm, weight was 64.9 kg, BMI was 24.9 kg/m^2, blood pressure was 110/65 mmHg and heart rate was 76 beats/min. Similar to her younger sister, no other physical abnormalities or complications were apparent. Fasting blood CPR was 1.06 ng/mL, CPI was 0.8, and 24-h UCPR was 37.5 μg/day at the time of onset, revealing that endogenous insulin secretory capacity remained present (Table 1). Islet autoantibody titers were 81.2 U/mL for GADA, < 0.6 U/mL for IA-2A, and 509 U/mL for ZnT8A, with negative results for ICA (Table 1). Both TgA and TPOA showed high values of 297 U/mL and 26 U/mL, respectively (Table 1). HLA showed A24 and disease-susceptible haplotypes DRB1* 0901-DQB1* 0303 [4] (Table 2). She was treated with insulin lispro at 8 units/day and glargine U100 at 9 units/day.

Insulin auto-antibody did not evaluate because it could not collect blood samples before using insulin.

	Younger sister	**Older sister**	**Reference value**
Age at onset (years)	**24**	**29**	
Sex	**Female**	**Female**	
GADA (U/mL)	791.6	81.2	< 5.0
IA-2A (U/mL)	6.2	< 0.6	< 0.6
ICA (JDF units)	negative	negative	negative
ZnT8A (U/mL)	406	509	< 15.0
TgA (U/mL)	19	297	< 28.0
TPOA (U/mL)	17	26	< 16.0
HbA1c at onset (%)	14.3	9.6	4.9-6.0
Fasting CPR at onset (ng/mL)	0.15	1.06	0.61-2.09
Fasting CPI at onset	0.2	0.8	-
24-h UCPR at onset (μg/day)	22	37.5	29.2-167.0

GADA, anti-glutamic acid decarboxylase antibody; IA-2A, anti-anti-insulinoma-associated protein-2 antibody; ICA, islet cell antibody; ZnT8A, zinc transporter 8 antibody; TgA, anti-thyroglobulin antibody; TPOA, anti-thyroperoxidase antibody; CPR, C-peptide immunoreactivity; CPI, CPR index; 24-h UCPR, 24-h urinary CPR. GADA, IA2A and ZnT8 were measured by enzyme-linked immunosorbent assay. ICA was measured by indirect method with immunofluorescent antibody. TgA and TPOA were measured by electrochemiluminscence immunoassay.

Table 1: Laboratory findings.

	Younger sister	**Older sister**
HLA-A	24:02/26:01	24:02/26:01
	A24/A26	A24/A26
HLA-B	35:01/39:01	39:01/40:06
	B35/B3901	B3901/B61
	Bw6/-	Bw6/-
HLA-C	03:03/07:02	07:02/08:01
	Cw9/Cw7	Cw7/Cw8
HLA-DRB1	08:02/09:01	09:01/-
	DR8/DR9	DR9/-
HLA-DRB3/4/5	4*01:03:02	4*01:03:02
	DR53/-	DR53/-
HLA-DQA1	03:01/03:02	03:02/-
	DQ8/DQ9	DQ9/-
HLA-DQB1	03:02/03:03	03:03/-
	DQ8/DQ9	DQ9/-
HLA-DPA1	02:02/-	01:03/02:02
HLA-DPB1	05:01/-	03:01/05:01
Haplotype	DRB1*0802-DQB1*0302 DRB1*0901-DQB1*0303	DRB1*0901-DQB1*0303

HLA, human leukocyte antigen

Table 2: HLA genotyping.

3. Discussion

The younger sister displayed different disease susceptibility HLA haplotypes (DRB1*0901-DQB1*0303/DRB1*0802-DQB1*0302) on both chromosomes, while the older sister had a disease susceptibility HLA haplotype (DRB1*0901-DQB1*0303/-) on one chromosome (Table 2). Furthermore, the younger sister was positive for GADA, IA-2A and ZnT8A, and endogenous insulin secretory capacity was depleted at the time of onset (Table 1). On the other hand, the older sister was positive only for GADA and ZnT8A, and the ability to secrete endogenous insulin at the onset remained relatively intact (Table 1).

3.1 HLA and endogenous insulin secretory capacity

Three subtypes of type 1 diabetes are known: acute onset; slowly progressive; and fulminant [9]. In addition, acute onset type 1 diabetes develops when the disease-susceptible HLA haplotype is present on both chromosomes, while slowly progressive type 1 diabetes can develop with the involvement of only one chromosome. That is, the HLA types of both subtypes are reported to be quantitatively different [10]. The younger sister, who had disease-susceptible HLA haplotypes on both chromosomes, had already been depleted of endogenous insulin secretory capacity by the time of onset (Tables 1, 2), suggesting a relatively rapid β-cell injury type. On the other hand, the

older sister, who had a disease-sensitive HLA haplotype on only one chromosome (Table 2), was considered to show a relatively slow type of β-cell injury, because the ability to secrete endogenous insulin was still present at onset (Table 1). However, Nakanishi et al. reported that HLA-A24, -DQA1*03, and -DR9 are involved in acute onset and early complete destruction of pancreatic β-cells [11], and both sisters showed these (Table 2), and the residual endogenous insulin secretory capacity of the older sister is considered likely to become depleted relatively early. On the other hand, HLA-A24 has also been reported to be associated with accelerated disease progression of type 1 diabetes, limited to relatives with HLA-DQ8 and positive results for anti-IA-2 antibody or ZnT8 antibody [12]. The lack of HLA-DQ8 in the older sister (Table 2) may be one factor contributing to the retention of endogenous insulin secretion compared to the younger sister.

3.2 Islet-associated autoantibodies and endogenous insulin secretory capacity

In the younger sister, islet autoantibodies were all positive except for ICA (Table 1). The frequency of positive results for the four types of islet autoantibodies has been shown to be significantly lower in adult-onset disease compared to the childhood-onset version [13]. Pancreatic beta-cell damage has also been reported to be more likely to progress in patients with multiple islet antibodies (GADA, IA-2A, and ZnT8A) [14]. This was considered to be one of the reasons why the younger sister showed greater pancreatic β-cytotoxicity than the older sister, who was positive for the two types of islet autoantibodies (Table 1). In addition, Yasui et al. have reported that GADA ≥28.0 U/mL (sensitivity 88.2%, specificity 91.7%), age at onset of diabetes <47 years (sensitivity 60.3%, specificity 78.0%), diabetes period <5 years until a GADA-positive finding (sensitivity 65.1%, specificity 67.1%), or fasting serum CPR <0.65 ng/ml (sensitivity 61.4%, specificity 97.6%) predict the need for insulin treatment in diabetic patients who were positive for GADA and had autoimmune thyroid disease [15]. The younger sister met all these conditions, while the older sister met the conditions other than those related to fasting serum CPR (Table 1), and both required insulin treatment. On the other hand, in addition to GADA titer, age of onset, disease duration and fasting serum CPR value, Tanaka et al. reported that a low BMI and positive ICA (IA-2A was detected as positive in analysis excluding ICA) is a risk factor for progression to an insulin-dependent state [16]. We speculated that the fact that only the younger sister showed IA-2A (Table 1) might have also influenced the difference in residual insulin secretory level between the younger and older sisters. Furthermore, in Japanese populations, ZnT8A has been shown to be present in 28% at the time of onset of type 1 diabetes [17], reportedly reflecting progression of the disease before and after diagnosis [18]. Since both sisters had ZnT8A (Table 1), the older sister appears likely to go through a progressive deterioration in the future. ZnT8A has also been reported as a marker leading to diabetic ketoacidosis at the onset of type 1 diabetes [19], but neither sister exhibited acidosis at onset.

A key limitation in this case report was that it was difficult to perform further detailed examinations and consideration, because HLA typing of family members other than the sisters had not been performed and no searches had been conducted for type 1 diabetes susceptibility genes other than HLA [20].

4. Conclusion

We experienced the Japanese cases of two sisters with type 1 diabetes. From our cases and existing reports, we reconfirmed that: 1) presence of HLA haplotypes for disease susceptibility on both chromosomes; 2) presence of HLA-DQ8 and HLA-A24, -DQA1*03 and -DR9; 3) higher titers of islet autoantibodies including IA-2A and ZnT8A may be involved in accelerating the progression of type 1 diabetes by enhancing the damage to pancreatic β-cells. In Japanese acute-onset type 1 diabetes that does not meet the above three conditions, protection of residual pancreatic β-cells by achieving more stringent glycemic control from the early stages of the onset may be able to maintain the honeymoon period longer.

Acknowledgments

We wish to thank HLA Laboratory, Kyoto, Japan, for the HLA genotyping, and SRL, Inc, Tokyo, Japan, for measurements of islet-related antibodies by Enzyme-linked immunosorbent assay, *Radioimmunoassay* or indirect methods with immunofluorescent antibody, and for measurements of TgA and TPOA by Electro chemiluminescence immunoassay. We also thank the patients for their permission to publish this manuscript. Furthermore, we acknowledge the medical editing services of Forte, Inc.

Compliance with Ethical Standards

Disclosure statement

There is nothing to disclose.

Human rights statement and informed consent

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions.

Consent for publication

Informed consent was obtained from the patients for publication of this case report.

Conflicts of interest

Yoshihiko Nishio has received honoraria for scientific lectures from Eli Lilly, Novo Nordisk Pharma and Sanofi, and a scholarship donation from Novo Nordisk Pharma. Koshi Kusumoto, Nobuyuki Koriyama, Nami Kojima and Maki Ikeda have nothing to disclose.

References

1. Onengut-Gumuscu S, Chen WM, Burren O, et al. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. Nat Genet 47 (2015): 381-386.

2. Ikegami H, Noso S, Babaya N, et al. Genetics and pathogenesis of type 1 diabetes: prospects for prevention and intervention. J Diabetes Investig 2 (2011): 415-420.
3. Todd JA, Walker NM, Cooper JD, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 39 (2007): 857-864.
4. Kawabata Y, Ikegami H, Kawaguchi Y, et al. Asian-specific HLA haplotypes reveal heterogeneity of the contribution of HLA-DR and -DQ haplotypes to susceptibility to type 1 diabetes. Diabetes 51 (2002):545-551.
5. Ikegami H and Ogihara T. Genetics of insulin-dependent diabetes mellitus. Endocr J 43 (1996): 605-613.
6. Kishi A, Kawabata Y, Ugi S, et al. The onset of diabetes in three out of four sisters: a Japanese family with type 1 diabetes. A case report. Endocr J 56 (2009): 767-772.
7. Ina Y, Kawabata Y, Sakamoto R, et al. Rare human leukocyte antigen genotype in two siblings with type 1 diabetes in a Japanese family clustered with type 1 diabetes. J Diabetes Investig 8 (2017): 762-765.
8. Olamoyegun MA, Ala OA. Type 1 diabetes in a Nigerian family - occurrence in three out of four siblings: A case report. World J Diabetes 10 (2019): 511-516.
9. Imagawa A, Hanafusa T, Miyagawa J, et al. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabets-related antibodies. N Engl J Med 342 (2000): 301-307.
10. Kawabata Y, Ikegami H, Awata T, et al. Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. Diabetologia 52 (2009): 2513-2521.
11. Nakanishi K, Inoko H. Combination of HLA-A24, -DQA1*03, and -DR9 contributes to acute-onset and early complete beta-cell destruction in type 1 diabetes: longitudinal study of residual beta-cell function. Diabetes 55 (2006): 1862-1868.
12. Balke EM, Balti EV, Van der Auwera B, et al. Accelerated progression to type 1 diabetes in the presence of HLA-A*24 and -B*18 is restricted to multiple islet autoantibody-positive individuals with distinct HLA-DQ and autoantibody risk profiles. Diabetes Care 41 (2018): 1076-1083.
13. Kawasaki E. Type 1 diabetes and autoimmunity. Clin Pediatr Endocrinol 23 (2014): 99-105.
14. Lampasona V, Petrone A, Tiberti C, et al. Zinc transporter 8 antibodies complement GAD and IA-2 antibodies in the identification and characterization of adult-onset autoimmune diabetes: non insulin requiring autoimmune diabetes (NIRAD) 4. Diabetes Care 33 (2010): 104-108.
15. Yasui J, Kawasaki E, Tanaka S, et al. Clinical and genetic characteristics of non-insulin-requiring glutamic acid decarboxylase (gad) autoantibody-positive diabetes: a nationwide survey in Japan. PLoS One 11 (2016): e0155643.doi:10.1371.
16. Tanaka S, Okubo M, Nagasawa K, et al. Predictive value of titer of GAD antibodies for further progression of beta cell dysfunction in slowly progressive insulin-dependent (type 1) diabetes (SPIDDM). Diabetol Int 7 (2015): 42-52.

17. Kawasaki E, Uga M, Nakamura K,et al. Association between anti-ZnT8 autoantibody specificities and SLC30A8 Arg325Trp variant in Japanese patients with type 1 diabetes. Diabetologia 51 (2008): 2299-2302.
18. Juusola M, Parkkola A, Härkönen T, et al. Positivity for zinc transporter 8 autoantibodies at diagnosis is subsequently associated with reduced β-cell function and higher exogenous insulin requirement in children and adolescents with type 1 diabetes. Diabetes Care 39 (2016):118-121.
19. Niechciał E, Rogowicz-Frontczak A, Piłaciński S,et al. Autoantibodies against zinc transporter 8 are related to age and metabolic state in patients with newly diagnosed autoimmune diabetes. Acta Diabetol 55 (2018): 287-294.
20. Johnson MB, Cerosaletti K, Flanagan S, et al. Genetic mechanisms highlight shared pathways for the pathogenesis of polygenic type 1 diabetes and monogenic autoimmune diabetes. Curr Diab Rep 19 (2019).

Citation: Koshi Kusumoto, Nobuyuki Koriyama, Nami Kojima, Maki Ikeda, Yoshihiko Nishio. Japanese Adult-Onset Type 1 Diabetic Sisters with Different Disease States: A Case Report. Archives of Clinical and Medical Case Reports 4 (2020): 699-706.