Review

Insulin autoimmune syndrome (Hirata Disease): Epidemiology in Asia including Japan

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Summary

As populations with a higher prevalence of HLADRB1*0406 was found to have a higher risk of development of insulin autoimmune syndrome (IAS), we showed clinical features of Asian and Japanese IAS. There was relatively female dominancy in the age distribution group of 20-49 year age at onset of the development of IAS. Forty two % of the Japanese IAS patients had received drugs or α-lipoic acid which contained the sulfhydryl group, while 81% of Asian IAS patients outside Japan had received methimazole or carbimazole ahead of development of IAS.

Introduction

Insulin autoimmune syndrome (IAS) was characterized by the combination of fasting hypoglycemia, high concentration of total serum insulin, presence of autoantibodies to native insulin in serum, and the striking association of HLA-DR4 (DRB1*0406 has a high titer of Odds ratio for the development). IAS is one of 2 types of autoimmune forms of hypoglycemia.

The first patient with IAS was reported by Hirata Y, et al. in 1970 (1). Since then, 197 patients with IAS from 1970 to 1992 were reported in 1994 (2). At the end of 2007, the records of a total of 325 patients were obtained from the first and the second nationwide surveys for spontaneous hypoglycemia, the database of Japan Centra Revuo Medicina, Medline and personal communications to us.

Another interesting point is that predisposition to IAS is significantly influenced by the ethic background of the subject, with East Asian people exhibiting a higher titer incidence than Caucasians. The extremely low prevalence of IAS among

Caucasians can be explained by the low prevalence of DRB1*0406 in this population (3). Only 58 non-Asian patients with IAS have been reported so far (4). On the hand, there were 21 Asian patients with IAS outside Japan, who were Chinese and Korean, obtained so far from the literature and personal communications to us.

Here, we show the epidemiology of IAS in Asia including Japan.

Onset age and sex distribution, duration of hypoglycemia

Age of onset and sex distribution of the 325 IAS cases in Japanese are listed in Table 1. Table 2 shows the clinical features of IAS in Asian excluding Japanese. Although the distribution of age at onset was wide in Japanese patients, the peak age of onset was 60-69 years for both sexes; there was no remarkable sex difference in the other age distribution except 20-49 year group, in which 62% were female patients with IAS.

According to the study from 1970 to 1992, there was no female dominancy except 20-29 year group in Japanese (2). It is attributable to that the 20-29 year group had a larger number of female patients with Graves' disease. Indeed, 17 (81%) of 21 patients with IAS in Asian outside Japan developed IAS with Graves' disease with the treatment of MTZ or CMZ (Carbimazole), which is converted to MTZ in the body and 9 (53%) of 17 patients belonged to the female 10-29 year group in Table 2. Such features may support evidence that methimazole for treatment of Graves' disease is strongly related to the development of IAS (5, 6).

After 2004, α-lipoic acid intake was found to be related to the development of

IAS (7). Table 3 shows the clinical features in IAS cases with α-lipoic acid intake in Japanese published from 2003 when the first case was reported by Hashinaga T, et al. to the end of 2007. There are 14 female patients among 17 with IAS and 7 among 17 (41%) belonged to the female 30-49 year group. In addition to methimazole, α-lipoic acid intake may accelerate the incidence of the development of IAS in female 20-49 year group, which means comparatively younger age.

The duration of the transient and spontaneous hypoglycemia was shown to be less than 1 month in approximately 30% of the patients, more than 1 month and less than 3 months in 40% of the patients (2). A few of the patients have continued mild hypoglycemic attacks for more than 1 year.

The geographic distribution of IAS in Japan showed no characteristic pattern in the areas of residence of the patients(5).

Drug exposure ahead of development of IAS and associated diseases

In addition to MTZ for the treatment of Graves' disease (6,7), α-mercaptopropionyl glycine (MPG) for the treatment of chronic hepatitis, dermatitis, cataract and rheumatoid arthritis, and glutathione (GTT) for urticaria, which contained the sulfhydryl (SH) group, were proposed to be related to the development of IAS (2). Forty two % (136/325) of Japanese IAS patients had received drugs with SH groups (8). After such drugs were discontinued, the hypoglycemic attacks subsided. There were 4 IAS patients who developed IAS at the second treatment after interruption of MTZ therapy, 1 IAS patient who developed the disease after the third challenge (after two interruptions of MTZ

therapy), and 1 IAS patient at both the first and the second MTZ treatment. Another 3 patients redeveloped IAS at MPG challenge (2). Such evidence may support the breakdown of T cell immunotolerance in the circumstance described above. In other words, it supports the "switch-on" of T cell immunoresponse in the circumstance with SH group exposure.

We propose a new concept of disease entitled "drug-induced insulin autoimmune syndrome" (8). Although MTZ had been a representative SH compound as a drug exposed before the development of IAS as described above, an IAS patient induced by α-lipoic acid was found in 2003 and an increasing number of α-lipoic acid-induced IAS have been recently remarkable (8). Among 56 IAS patients from 2003 to 2007, MTZ for Graves' disease was prescribed for 11 IAS patients and α-lipoic acid for dieting or anti-aging supplement for 17 IAS patients (8) (Table 2). After α - lipoic acid intake were discontinued, the hypoglycemic attacks subsided. SH-group compounds such as MTZ and dihydrolipoic acid converted from α-lipoic acid may cleave the disulfide bond of insulin molecule in vivo and allow the specific HLA complex on antigen-presenting cells (8).

On the other hand, there was no Asian IAS patient with a history of taking α -lipoic acid outside Japan (Table 3). Seventeen (81%) of 21 IAS patients have associated with Graves' disease with a history of taking MTZ or CMZ. There might be 2 reasons that MTZ or CMZ has been the major pill for the treatment of Graves' disease and there has not been a trend or in the fashion of α-lipoic acid treatment or intake for supplements.

Two group of IAS defined by clonality of insulin autoantibodies

Insulin autoantibodies from IAS patients were classified as polyclonal or monoclonal on the basis of affinity curves for binding to human insulin (Scatchard analysis) and presence of solitary light chains. So far, in 3 among 330 Japanese IAS patients, the insulin autoantibodies were shown to have a single binding affinity to human insulin in a Scatchard analysis, which means monoclonality (9,10,11). Japanese IAS patients in general showed polyclonal autoantibodies to human insulin. Two Korean (3 and 4 in Table 2), and 2 Chinese (5 and 21 in Table 2) IAS patients were shown to possess polyclonal insulin autoantibodies. Other patients in Table 2 seem to have polyclonal because the hypoglycemic attacks were reported to be subsided after MTZ/CMZ treatment were discontinued. It is likely that the incidence of polyclonal IAS is relatively high among East Asians including Japan, whereas monoclonal IAS is more prevalent in Caucasians (12).

DR gene products in the presentation of human insulin antigen

As we reported previously, 96 % (48/50) of Japanese IAS patients had DR4 (Odds ratio, 39.9, $p<10^{-4}$). DR9 was positive in 12 (24%) Japanese IAS patients, though, this was not significant compared with Japanese healthy controls (Odds ratio, 0.8, $p>0.65$) (12).

The 48 DR4-positive Japanese IAS polyclonal responders consisted of 42 DRB1*0406-positive (Odds ratio, 56.6), 5 DRB1*0403-positive (Odds ratio, 1.6), and 1 DRB1*0407-positive patients (Odds ratio, 1.1) (11). All 48 DR4-positive Japanese IAS polyclonal responders possessed DQA1*0301/DQB1*0302 regardless

of the differences in DR4 alleles. The two Korean and 3 Chinese IAS polyclonal responders were also positive for DRB1*0406/DQA1*0301/DQB1*0302 (patient 3, 4, 5 and 21 in Table 2). Patient 18 in Table 2 was shown to possess DRB1*0406 (13). Thus, the DR4-positive IAS polyclonal responders possess DRB1*0406, DRB1*0403, or DRB1*0407 for DR4 alleles, and DQA1*0301/DQB1*0302 or DQA1*0301/DQB1*0301 for DQ3 alleles.

The differences in DQβ1 alleles encoding DQ3 among the IAS polyclonal responders suggest that DQ α and DQ β chains are not important in the development of IAS. We showed that T cells from polyclonal IAS patients with DRB1*0406/DQA1*0301/DQB1*0302 alleles proliferated in the presence of autologous antigen-presenting cells that had been exposed to 40 uM human insulin (14). The proliferative response of T cells was completely blocked by anti-HLA-DR but not by anti-HLA-DQ monoclonal antibodies (15). Moreover, experiments with DRB1*0406 transfectants supported the view that DR gene products participate in the presentation of human insulin antigens (15).

The HLA-DRβ1-chains encoded by DRB1*0406, DRB1*0403, and DRB1*0407 share a sequence motif (Leu-Leu-Glu-Gln-Arg-Arg-Ala-Glu) that spans the amino acid residues 67 - 74 of the third hypervariable region. The two DR9/DQ3 Japanese IAS polyclonal responders were DRB1*0901/ DQA1*0301/DQB1*0303 homozygous. The products of DRB1*0406, DRB1*0403, and DRB1*0901 share the sequence motif Arg-Arg-Ala-Glu, corresponding to amino acid residues 71 - 74 of the DR β1-chain. Comparison of this region of the DRβ1-chain and other DRB1 allele products reveals that Arg^{71} and especially Glu^{74} may be important for polyclonal insulin autoantibody production in IAS, whereas residues 72 and 73

(Arg-Ala) are common in most DRB1 molecule. Therefore, individuals with DRB1*0406 may have a risk of developing IAS.

Is there DR4 allele-difference between IAS patients with MTZ exposure and with α-lipoic acid exposure? As shown previously, all of Japanese IAS patients with MTZ exposure possessed DRB1*0406 (7) and 5 Asian IAS patients with MTZ exposure outside Japan possessed DRB1*0406, while the remaining 13 with MTZ exposure had no information so far (Table 2). On the other hand, there are the information of DRB1 allele in 12 among 17 IAS patients with α-lipoic acid exposure (Table 3), who consisted of 10 DRB1*0406-positive and 2 DRB1*0403-positive patients. As α-lipoic acid has a strong reducing ability to protect peripheral cells from oxidative stress, individuals with DRB1*0403, if they would take α-lipoic acid, might be under the condition which is more risky of developing IAS compared to that without α-lipoic acid exposure. However, there are IAS DRB1*0403- and DRB1*0407-positive patients without any drug or supplement exposure information and there are a few patients who possess DRB1*0404 (16) or DRB1*1405 (17) without the exposure of MTZ or α-lipoic acid which are a representative SH compound with strong reducing ability. Such findings will raise a possibility of another gene product which is more associated with IAS than DRB1*0406.

Conflict of interest

There are no conflicts of interest.

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Table 1

Age at onset and sex distribution in Japanese IAS patients, 1970-2007

Age at onset	IAS patient Male(n)	Female(n)	Total
0 - 9	0	2	2
10 - 19	1	1	2
20 - 29	6	18	24
30 - 39	12	16	28
40 - 49	22	31	53
50 - 59	32	32	64
60 - 69	39	42	81
70 - 79	34	22	56
80 - 89	4	11	15
Total	150	175	325

Table 2

Clinical features in IAS cases in East Asians except Japanese

patient	Age	Sex	Disease/Drug	Race	DRB1*	Reference	Year
1	52	M	Vasculitis ?	Chinese	-	18	1984
2	48	F	Graves'/MTZ	Chinese	-	18	1984
3	31	F	Graves'/MTZ	Korean	0406@	19	1987
4	61	F	Graves'/MTZ	Korean	0406@	19	1987
5	18	F	Graves'/MTZ	Chinese	0406@	20	1987
6	26	F	Graves'/ MTZ/CMZ	Chinese	-	21	1988
7	27	F	Graves'/ MTZ/CMZ	Chinese	-	21	1988
8	27	M	Graves'/ MTZ/CMZ	Chinese	-	21	1988
9	38	M	Graves'/MTZ/CMZ	Chinese	-	21	1988
10	31	F	Graves'/MTZ/CMZ	Chinese	-	21	1988
11	36	F	Graves'/MTZ/CMZ	Chinese	-	21	1988
12	27	F	Graves'/CMZ	Chinese	-	22	1988
13	67	F	-	Chinese	-	23	1990
14	28	F	Graves'/MTZ	Chinese	-	23	1990
15	26	F	Graves'/MTZ	Chinese	-	23	1990
16	24	F	Graves'/MTZ	Chinese	-	23	1990
17	34	M	Graves'/MTZ	Chinese	-	24	1994
18	44	F	Graves'/MTZ	Chinese	0406	13	2005
19	-	-	Pulmonary TB/INH	Chinese	-	25	2005
20	21	F	Graves'/MTZ	Chinese	0406	unpublished#	
21	11	F	Hashimoto/Thyradin	Chinese	0406	unpublished+	

unpublished#, kindly provided by Dr. Lin in Taiwan.

unpublished+, kindly provided by Dr. Wacharasindhu in Thailand.

@, shown in Ref.11.

Table 3

Clinical features in IAS cases with α lipoic acid intake in Japanese published from 2003 to the end of 2007

patient	Age	Sex	IRI μU/ml	% binding	HLADRB1	Author's name
1	55	F	8,149	95	0406	Hashinaga.et al 2003
2	44	F	538	96	0406/0901	Takeda et al. 2006 Furukawa et al. 2007
3	67	F	787	96	-	Kamiya et al. 2006
4	66	M	660	88	0406	Nishikawa et al 2006
5	32	F	5,860	82	0406	Sekimoto et al. 2006 Ishida et al. 2007
6	49	F	240↑	66.9	0406	Takanashi et al. 2006*
7	34	F	400	93	0406	Yoshioka et al. 2006*
8	64	F	126	93	DR4#	Kurashiki et al. 2006
9	34	F	518	95	0406	Nakajima et al. 2007
10	55	M	2,531	93.3	0406	Takeuchi et al 2007
11	36	F	64.8	91	-	Yoshida et al. 2007
12	35	M	1,949	positive	0406	Sasaki et al. 2007
13	36	F	995	82	-	Ogou et al. 2007
14	40	F	4,320	86	0403	Kudo et al. 2007
15	48	F	119.2	92	0406	Matsui et al. 2007
16	45	F	13,240	81.2	0403	Yamada et al. 2007
17	41	F	285.3	90	-	Suzuki et al. 2007

* The α lipoic acid exposure and DRB1*0406 was found after reported.
# There is no data of DRB1 allele.
HLADRB1 alleles which have been found to be important in IAS are shown.