Diabetol Int (2010) 1:21–25
DOI 10.1007/s13340-010-0001-z

REVIEW ARTICLE

Insulin autoimmune syndrome (Hirata disease): epidemiology in Asia, including Japan

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Received: 11 May 2010 / Accepted: 8 June 2010 / Published online: 10 September 2010

Abstract As populations with a higher prevalence of HLADRB1*0406 have been found to have a higher risk of developing insulin autoimmune syndrome (IAS), we report here the clinical features of Asian and Japanese IAS. There was female dominance in the 20- to 49-year-old age group at the onset of IAS development. Forty-two percent of Japanese IAS patients had received drugs or α-lipoic acid containing the sulfhydryl group, while 81% of Asian IAS patients outside Japan had received methimazole or carbimazole before the development of IAS.

Keywords Hypoglycemia · Insulin autoimmune syndrome · Methimazole · Alpha-lipoic acid · HLA

Introduction

Insulin autoimmune syndrome (IAS) is characterized by a combination of fasting hypoglycemia, a high concentration of total serum insulin, the presence of autoantibodies to native insulin in serum, and a strong association with HLA-DR4 (DRB1*0406 is associated with a high odds ratio for the development of IAS). IAS is one of two autoimmune forms of hypoglycemia.

The first patient with IAS was reported by Hirata 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 Japana Centra Revuo Medicina, Medline, and through personal communications with us.

Another interesting point is that predisposition to IAS is significantly influenced by the ethnic background of the subject, with East Asian people exhibiting a higher 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 other hand, 21 Asian patients (Chinese and Korean) with IAS outside Japan have been obtained so far from the literature and through personal communications with us.

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

Age of onset and sex distributions and duration of hypoglycemia

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

According to the study covering 1970 to 1992, there was no female dominance except in the 20- to 29-year group in Japanese [2]. This can be attributed to the fact that the 20- to 29-year group had a larger number of female patients with Graves' disease. Indeed, 17 (81%) of the 21 Asian (except for Japanese) patients with IAS developed IAS with Graves' disease with MTZ or CMZ (carbimazole,

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which is converted to MTZ in the body) treatment, and 9 (53%) of these 17 patients were females who were 10–29 years of age. Such features may provide support for the idea that the use of methimazole to treat 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 of Japanese IAS cases with α-lipoic acid intake from 2003 (when the first case was reported by Hashinaga et al.) to the end of 2007. There are 14 female patients among the 17 with IAS, and 7 of these (41% of all female patients with IAS) belonged to the female 30- to 49-year group. In addition to methimazole, α-lipoic acid intake may accelerate the development of IAS in the 20- to 49-year-old female group, leading to a comparatively young age of IAS development.

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

The geographic distribution of the IAS cases in Japan showed no characteristic pattern in terms of the areas of residence of the patients [5].

Table 1 Age at onset and sex distributions for Japanese IAS patients, 1970–2007

Age at onset	IAS patients		
	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

Drug exposure before the 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

Table 2 Clinical features of East Asian IAS cases (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[a]	[19]	1987
4	61	F	Graves'/MTZ	Korean	0406[a]	[19]	1987
5	18	F	Graves'/MTZ	Chinese	0406[a]	[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	[b]	
21	11	F	Hashimoto/Thyradin	Chinese	0406	[c]	

[a] Shown in [11]

[b] Unpublished; kindly provided by Dr. Lin in Taiwan

[c] Unpublished; kindly provided by Dr. Wacharasindhu in Thailand

Table 3 Clinical features of Japanese IAS cases with α-lipoic acid intake reported 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)[b]
7	34	F	400	93	0406	Yoshioka et al. (2006)[b]
8	64	F	126	93	DR4[a]	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)

HLADRB1 alleles that have been found to be important in IAS are shown

[a] There are no data for the DRB1 allele

[b] The α-lipoic acid exposure and DRB1*0406 was found after the case reports

of chronic hepatitis, dermatitis, cataract and rheumatoid arthritis) and glutathione (GTT; for urticaria), which both also contain the sulfhydryl (SH) group, were proposed to be related to the development of IAS [2]. Forty-two percent (136/325) of the Japanese IAS patients had received drugs with SH groups [8]. When these drugs were discontinued, the hypoglycemic attacks subsided. There were 4 IAS patients who developed IAS during the second treatment, after the MTZ therapy had been interrupted, 1 IAS patient who developed the disease after the third challenge (after 2 interruptions of MTZ therapy), and 1 patient who developed it with both the first and the second MTZ treatments. Another 3 patients redeveloped IAS upon MPG challenge [2]. This evidence may support the breakdown of T cell immunotolerance according to the circumstances described above; in other words, it indicates that the T cell immunoresponse may be switched on by exposure to a drug with an SH group.

We propose a new disease concept termed "drug-induced insulin autoimmune syndrome" [8]. Although it has been reported previously that patients developed IAS after exposure to MTZ, a drug compound with an SH group, as described above, the induction of IAS in a patient by α-lipoic acid was noted in 2003, and there have been an increasing number of α-lipoic acid-induced IAS cases recently [8]. Among 56 IAS patients from 2003 to 2007, MTZ was prescribed for Graves' disease in 11 IAS patients and α-lipoic acid was used as a dieting or anti-aging supplement in 17 IAS patients [8] (Table 2). After α-lipoic acid intake was discontinued, the hypoglycemic attacks subsided. SH-group compounds such as MTZ and dihydrolipoic acid (deriving from α-lipoic acid) may cleave the disulfide bond of the insulin molecule in vivo and allow the specific HLA complex on antigen-presenting cells to bind the insulin fragments [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 the 21 IAS patients have Graves' disease associated with a history of taking MTZ or CMZ. There could be two reasons for this: MTZ and CMZ have been the major drugs used to treat Graves' disease, and α-lipoic acid treatments or supplements have not been very fashionable.

Two IAS groups defined by the 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 the presence of solitary light chains. The insulin autoantibodies in 3 among 330 Japanese IAS patients were shown to have a single binding affinity to human insulin in a Scatchard analysis, implying monoclonality [9–11]. Japanese IAS patients in general showed polyclonal autoantibodies to

human insulin. Two Korean (patients 3 and 4 in Table 2), and 2 Chinese (patients 5 and 21 in Table 2) IAS patients were shown to possess polyclonal insulin autoantibodies. Other patients in Table 2 seem to have polyclonal autoantibodies to human insulin because the hypoglycemic attacks were reported to subside after the MTZ/CMZ treatment was discontinued. It is likely that the incidence of polyclonal IAS is relatively high among East Asians, including Japanese, 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, although this was not a significant difference from 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 2 Korean and 3 Chinese IAS polyclonal responders were also positive for DRB1 *0406/DQA1*0301/DQB1*0302 (patients 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 the DQβ1 alleles encoding DQ3 among the IAS polyclonal responders suggest that the 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 μM 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 DRβ1 chain. Comparison of this region of the DRβ1 chain with 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 molecules. Therefore, individuals with DRB1*0406 may be at risk of developing IAS.

Is there a DR4 allele difference between patients who develop IAS following MTZ exposure and those who develop IAS after α-lipoic acid exposure? As shown previously, all of the Japanese IAS patients who were exposed to MTZ possessed DRB1*0406 [7], and 5 Asian (not Japanese) IAS patients who were exposed to MTZ outside Japan possessed DRB1*0406, while there is currently no relevant information on the remaining 13 who had been exposed to MTZ (Table 2). On the other hand, there is information on the DRB1 allele in 12 of the 17 IAS patients exposed to α-lipoic acid (Table 3): they consisted of 10 DRB1*0406-positive and 2 DRB1*0403-positive patients. As α-lipoic acid has a strong reducing ability that can protect peripheral cells from oxidative stress, individuals with DRB1*0403, if they were to take α-lipoic acid, may be at greater risk of developing IAS than if they were not exposed to α-lipoic acid. However, there are DRB1*0403- and DRB1*0407-positive IAS patients for whom there is no information on their drug or supplement exposure, and there are a few IAS patients who possess DRB1*0404 [16] or DRB1*1405 [17] and were not exposed to MTZ or α-lipoic acid. Such findings raise the possibility that there is 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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