being injected with gold thioglucose into her hips for the treatment of bronchial asthma. Blood samples had been occasionally taken before and after the excision operation of hip granulomas at the gold-thioglucose injection sites, as shown in Figure 1. At time A in 1983, she experienced frequent hypoglycemic attacks. For the treatment of IAS, she was administered a corticosteroid at time B in 1984. The steroid (prednisolone) controlled the hypoglycemic attacks for a while and was then tapered off. Ten months later, she fell into a coma induced by hypoglycemia at time C in 1985. Time D in 1986 was just before the first operation for resection of her hip granulomas at the gold-thioglucose injection sites. Time E was just after the second operation for hip granuloma resection.

75-g oral glucose load

After fasting for 12 hours, a 75-g oral glucose load was given. Immunoreactive insulin (IRI) and C-reactive peptide (CPR) were determined in duplicate by double-antibody R1As using a "Shionogi Insulin Kit" (Osaka, Japan) and C-peptide kit "Daiichi III" (Tokyo, Japan), respectively. Free IRI was measured after the precipitation of antibody-bound insulin with polyethylene glycol (PEG). Total IRI was measured by acidification of the serum to dissociate bound insulin, followed by assay with the insulin kit.

Scatchard analysis using human insulin

Serum deinsulinized with dexran-coated charcoal[8] was used for the Scatchard analysis[9]. The serum was incubated with 100 ul of ^{125}I-human insulin (1.2×10^4 cpm/30–40 pg of human insulin/tube, Amersham, Buckinghamshire, U.K.) in the presence of 100 ul of serial concentrations of human insulin solution. After precipitation with PEG 6000, the radioactivity of the pellets was counted with an automatic gamma counter.

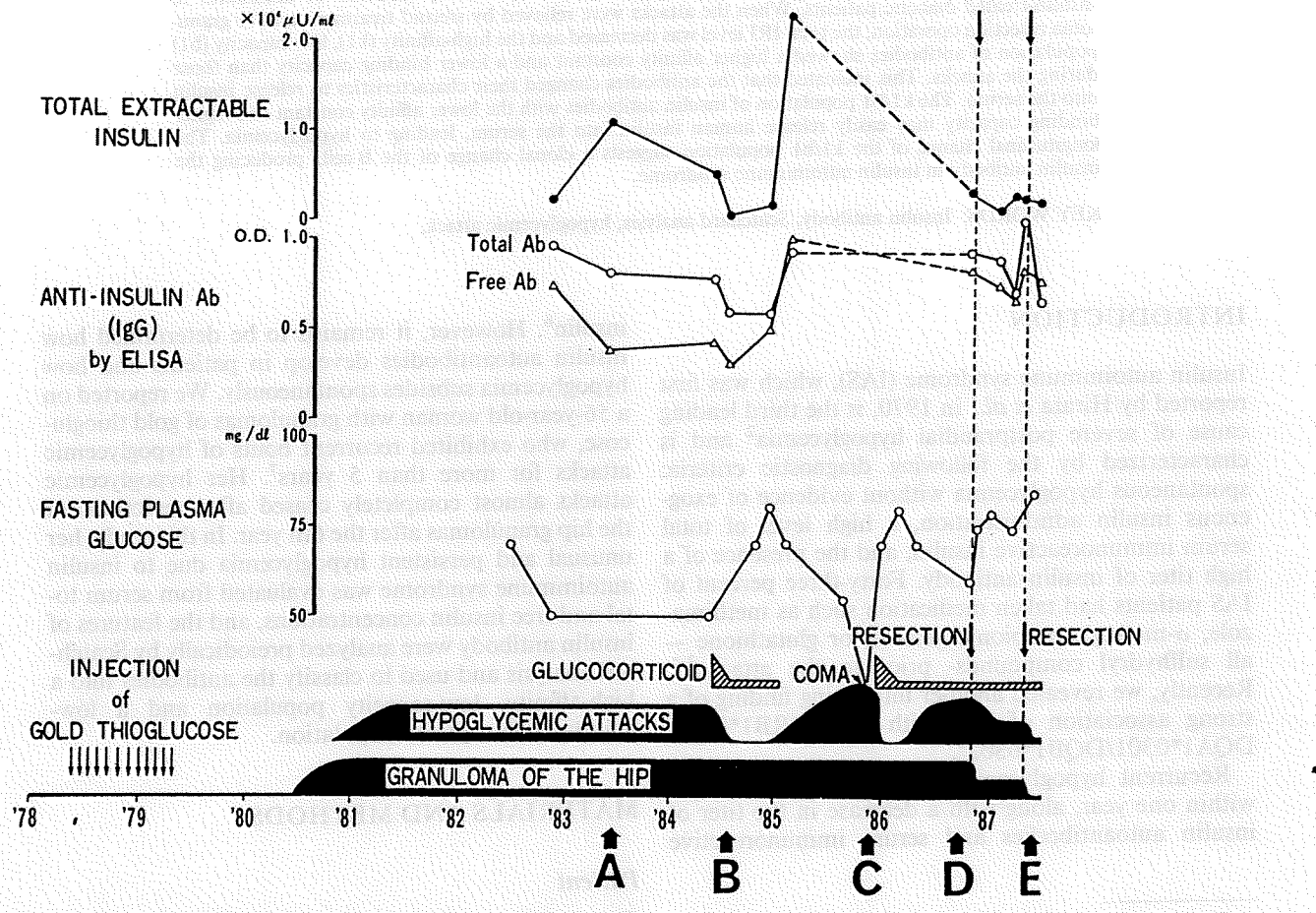

Figure 1 Profile of the clinical course of the patient. A, in 1983 when she experienced severe hypoglycemic attacks; B, when she received steroid treatment; C, when she fell into a coma induced by hypoglycemia; D, just before the first operation; and E, just after the second operation.

RESULTS

Figure 1 shows a profile of the clinical course of the patient. At time A, total IRI was found to be 9091 uU/ml. Around time B, total IRI was decreased to 1000 uU/ml after steroid treatment. At time C, the patient fell into a hypoglycemic coma with total IRI of 3500 uU/ml. After the first and second resections of gold thioglucose, fasting plasma glucose was increased constantly and the total IRI showed a tendency to decrease.

Figure 2 shows the Scatchard plots of insulin antibodies in sera collected at those five times. Table 1 shows the k1, b1, k2 and b2 value for each Scatchard analysis. Insulin antibodies in insulin-treated diabetic patients were also analyzed by Scatchard analysis for comparison with the data at times A to E. Before prednisolone treatment, k1 and b1 were 0.085×10^8 L/mole and 17.5×10^{-8} mole/L (A). After the hypoglycemic attacks had been controlled with prednisolone, the k1 value increased and the b1 value decreased (B). When the attacks recurred in 1985, the k1 value decreased to 0.074×10^8 L/mole and the b1 value increased to 22.0×10^{-8} mole/L (C). Before the first operation, the k1 value was 0.194×10^8 L/mole and b1 value increased to 24.5×10^{-8} mole/L (D). Then, after the granuloma was partly removed, the attacks ceased. Time E was just after the second operation to resect the hip granulomas. Most of the granulomatous tissue could be removed from her hip by the two operations. Again the k1 value increased and the b1 value decreased (E). Thus, the k1 value was higher and the b1 value was lower when hypoglycemia was relieved. When hypoglycemia worsened, the k1 value was lower and the b1 value was higher. However, the Scatchard analysis of insulin antibody showed that all values of k1 were lower and all values of b1 were higher than the respective values in insulin-treated diabetics throughout the clinical course.

Figure 3 shows results of a 75-g glucose tolerance test before the first resection operation at time D, which indicate a hyperglycemic response to glucose load. The serum total IRI concentration was increased almost 1.7-fold after 2 hours, from 2225 to 3805 uU/ml. The serum CPR concentration was increased 8-fold for the same interval, from 2.1 to 16.8 ng/ml. Subsequently, the plasma glucose concentration declined, reaching a value of 38 mg/dl after a further 2.5 hours. Both the total IRI and CPR declined during these 2.5 hours. At this time point, CPR was decreased 2.71-fold from 16.8 to 6.2 ng/ml, whereas total IRI was decreased 1.62-fold from 3805 to 2350 uU/ml, suggesting a delay in insulin clearance. The rate of decrease of free IRI was slower than that of CPR, suggesting the supplement of free insulin probably through the release of the bound insulin.

DISCUSSION

We previously described the profile of an unusual case of presistent hypoglycemia, which was considered to be induced by gold-thioglucose granuloma. The clinical picture of recurrent postprandial hypoglycemia with findings of extremely elevated serum IRI was indistinguishable from that of insulin autoimmune syndrome (IAS). For the treatment of the hypoglycemia, the patient received a steroid, resulting in relief of hypoglycemia. However, termination of steroid therapy resulted in a hypoglycemic coma. Although steroid treatment was recommended for effectively relieving hypoglycemia, gold thioglucose granuloma was suspected to be related to the persistent hypoglycemia. Resection of the gold-thioglucose granulomas performed twice successfully relieved her hypoglycemia.

Scatchard analyses were performed periodically to demonstrate the relationship between the hypoglycemia and the presence of the insulin antibodies with high-affinity (k1) and low-capacity (b1) and low-affinity (k2) and high-capacity (b2). As Table 1 shows,

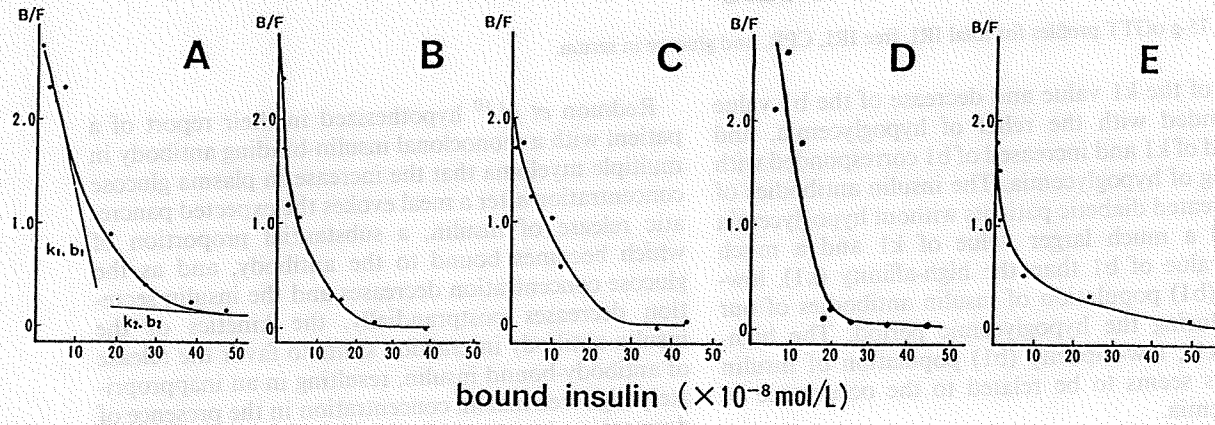

Figure 2 Scatchard analysis series for times A to E.

Table 1 Results of Scatchard analysis at each stage

	k1 $\times 10^8$ L/mole	b1 $\times 10^{-8}$ mole/L	k2 $\times 10^8$ L/mole	b2 $\times 10^{-8}$ mole/L
Time code of the patient				
A	0.085	17.5	0.0012	106.7
B	0.914	4.0	0.0009	20.7
C	0.074	22.0	0.0179	384.6
D	0.194	24.5	0.0034	164.7
E	0.474	7.0	0.0068	53.8
Five insulin-treated diabetic patients				
F	1.65	1.1	0.0297	6.3
G	1.45	0.4	0.0125	12.5
H	1.48	0.08	0.0006	151.2
I	4.02	0.18	0.0328	2.3
J	7.11	0.12	0.0334	4.7

A to E are the time codes shown in Figure 1. Data of F to J were obtained from Scatchard analyses using sera containing insulin antibody of five insulin-treated diabetic patients without hypoglycemia.

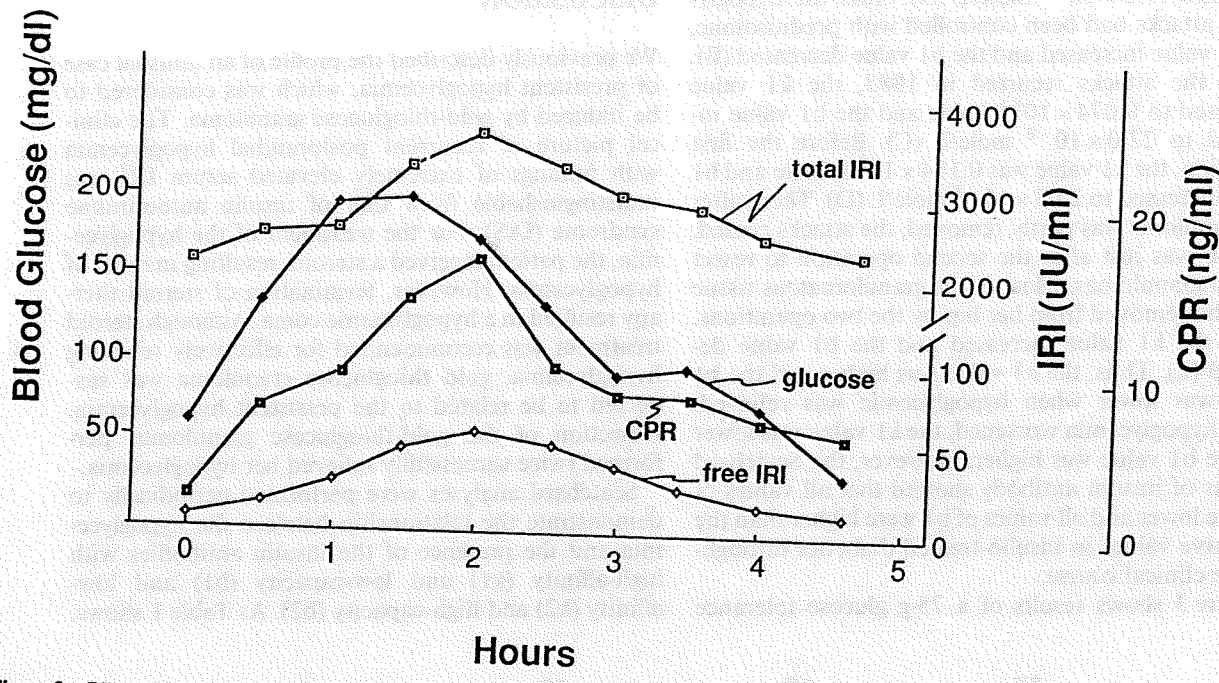

Figure 3 75-g oGTT profiles for total IRI, free IRI, CPR, and glucose in serum.

increase of the k1 value and decrease of the b1 value corresponded with the relief of hypoglycemia, and decreased of k1 and increased of b1 corresponded with worsening of hypoglycemia. The insulin antibodies of insulin-treated diabetic patients without hypoglycemia exhibited a much larger value of k1 and a much smaller value of b1 than the high-affinity (k1), low-capacity (b1) population of insulin antibodies of our patient during the hypoglycemic period. The high-affinity (k1), low-capacity (b1) population of insulin antibodies seems to be related to the occurrence of hypoglycemia.

Redmon *et al.*[10] hypothesized in their report of a patient with a monoclonal insulin-binding antibody in multiple myeloma that the increase in plasma glucose concentration after a meal evokes the expected pancreatic release of insulin, a substantial proportion of which becomes bound to the antibody, and as the glucose concentration decreases and the insulin secretion decreases postprandially, the kinetics of the insulin-antibody interaction shifts to favor the release of antibody-bound insulin, resulting in an inappropriately high free insulin concentration in the presence of decreasing glucose concentration. The results of the

75-g glucose tolerance test shown in Figure 3 in this study support their hypothesis. Such kinetics may support an equilibrium between human insulin (I), free insulin antibodies (Ab), and insulin antibodies bound to human insulin (I + Ab).

$$(I) + (Ab) \rightleftarrows (I + Ab)$$

With increasing blood glucose, human insulin will become the form bound to insulin antibodies, which shifts the kinetics to the right. When the insulin antibodies are saturated with human insulin, the kinetics shifts to the left, resulting in hypoglycemia due to the presence of a large amount of free insulin in the serum. When the high-affinity, low-capacity population of the insulin antibodies has a relatively low affinity constant and high-capacity binding, such an equilibrium seems to be established.

Other candidates, in addition to an elevated k1 value, are suggested to relieve or prevent hypoglycemia: for example, disappearance of insulin antibody, production of anti-idiotypic antibody against the insulin antibody, the proliferation of suppresser T cells, and the disappearance of certain adjuvants or immune modulators related to the production of insulin antibody. In general, 43% of IAS patients with insulin autoimmune syndrome had received methimazole, α-mercaptopropionyl glycine, or glutathione, which are all sulfhydryl compounds, for treatment of associated diseases[6]. After termination of therapy with these drugs, hypoglycemia was relieved within 4 to 5 days, and the values of total and free IRI also gradually decreased monthly (11–13). Hypoglycemia in our patient was relieved after resection of gold-thioglucose granulomas. The drugs described above may be strongly related to the development of IAS.

We recently revealed a strong association of insulin autoimmune syndrome with HLA-DR4 carrying DRB1*0406/DQA1*0301/DQB1*0302[5]. Graves' disease patients treated with methimazole developed insulin autoimmune syndrome on the base of HLA-Bw62/Cw4/DR4/DQ3 carrying DRB1*0406/DQA1*0301/DQB1*0302[14]. Our patient possessed HLA-Bw62/Cw4/DR4/DQw3 carrying DRB1*0406/DQA1*0301/DQB1*0302[5]. Therefore, gold thioglucose may be related to the production of insulin autoantibody, acting as a modifier of the immune system under HLA-DRB1*0406/DQA1*0301/DQB1*0302 restriction similar to methimazole administered for Graves' disease. Unfortunately, lymphocytes involved in the hip granulomas could not be detected as producing insulin autoantibodies (data not shown).

As we reported previously, dithiothreitol (DTT), which acts via the cleavage of one or more disulfide bonds in insulin, accelerated T cell proliferation in the presence of DRB1*0406-transfected L cells and human insulin[15], giving support to the hypotheses that such a sulfhydryl compound may present a new epitope for autoantigen to self-T cells. Methimazole, glutathione, and α-methylpropionyl glycine are all sulfhydryl compounds: therefore, a new autoantigen epitope is assumed to be exposed, leading to development of insulin autoimmune syndrome. On the other hand, gold thioglucose is not a sulfhydryl compound. In an electron micrograph showing a portion of the resected granuloma[7], the granuloma was still in the active phase of inflammation, and lysosomes containing gold particles were still being freely discharged from the ruptured macrophages. Since this indicated that the local inflammation had continued for more than 10 years, lysosomal enzymes could expose a certain epitope of human insulin to the autoantigen.

In general, insulin autoantibodies in insulin autoimmune syndrome are polyclonal[16]. The longitudinal change of the k1/b1 population of insulin antibodies suggests a clonal change of the B cells producing the insulin antibody. Bad and good episodes in autoimmune diseases may be explained in terms of a clonal change of B cells producing the autoantibody. Further investigation is needed to determine the mechanism of the clonal change of B cells producing the insulin autoantibody in insulin autoimmune syndrome.

Acknowledgements

This study was supported in part by the Scientific Research Fund from the Ministry of Education, Science and Culture of Japan, a grant from Japan Diabetes Foundation, and a grant from Takako Satake Memorial Foundation for Medical Research.

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DIABETES RESEARCH AND CLINICAL PRACTICE 83 (2009) e19–e20

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Brief report

Drug-induced insulin autoimmune syndrome

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ARTICLE INFO

Article history:
Received 3 September 2008
Received in revised form
3 September 2008
Accepted 31 October 2008
Published on line 12 December 2008

Keywords:
Insulin autoimmune syndrome
Hypoglycemia
Sulphydryl compounds
Alpha lipoic acid

ABSTRACT

Although insulin autoimmune syndrome (IAS) was found to be strongly related with methimazole, rapidly increasing numbers of cases with alpha lipoic acid-induced IAS have been confirmed to be reported since 2003. As alpha lipoic acid has gained popularity as a supplement for dieting and anti-aging, a warning should be issued.

The insulin autoimmune syndrome (IAS), or Hirata's disease, is characterized by the combination of fasting hypoglycemia, high concentration of total serum immunoreative insulin, and presence of autoantibodies to native human insulin in serum [1]. In addition, IAS has a striking association with HLA-DR4 (mainly with DRB1*0406 and sometimes with DRB1*0403 and DRB1*0407) [2,3], which showed that glutamate at position 74 in the HLA-DR 1 molecules was presumed to be essential to the production of polyclonal insulin autoantibody in IAS [2]. Between 1970 [1] and September of 2007, the number of spontaneous hypoglycemia cases caused by IAS reported to us was up to 380.

Another characteristic has been observed in the medication at the onset of IAS as Hirata already mentioned a relationship between IAS and methimazole [4]. The drugs are listed in Table 1 which were given to cases at the onset of IAS at the end of September of 2007. All of the drugs are sulphydryl compounds which are also reducing compounds. There have been reports of IAS outside Japan which were also associated with sulphydryl compounds: pyritinol for rheumatoid arthritis (Archambeaud-Mouverouz F. et al. 1988), Imipenem (beta-lactam antibiotic) for urosepsis (Lidar M. et al. 1999), and Penicilline G (beta-lactam antibiotic) for tonsillitis (Cavaco B. et al. 2001) except those listed in Table 1.

In 2003, a case with IAS which was possibly induced by an alpha lipoic acid was reported for the first time at the Kyushu local meeting of Japan Diabetes Society by Hashinaga T, et al. An increasing number of cases with alpha lipoic acid-induced IAS [5–7] have been recently remarkable. There are 56 IAS case reports in the database of Japan Centra Revuo Medicina between 2004 and September of 2007. Among 56 cases, methimazole for Graves' disease was prescribed for 11 cases, Tiopronin for one, Loxoprofen for one, and alpha lipoic acid for 17 cases. Also, garlic might have been given (containing S-allyl-mercapto-cystein which has s–s bond) to one case. Some of polyclonal insulin autoantibodies were served for Scatchard

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0168-8227/$ – see front matter
doi:10.1016/j.diabres.2008.10.015

Table 1 – Drugs exposure ahead of development of IAS and associated diseases from 1970 to September 2007 in Japan.

Drugs	Diseases	n
Methimazole*	Graves' disease	63
Alfa-mercaptopropionyl glycine (tiopronin)*	Chronic liver function/cataract/dermatitis/rheumatoid arthritis	45
Glutathione*	Urticaria	8
Gold thioglucose*	Bronchial asthma	1
Captopril*	Hypertension	1
Penicillamine*	Rheumatoid arthritis	1
Acegratone	Urinary balder carcinoma	1
Steroid	Polymyositis	1
Interferon-alfa	Renal cell carcinoma	1
Loxoprofen sodium	Rheumatoid polymyositis/lumbar pain	2
Alfa lipoic acid*	Dieting/anti-aging supplement	17
Miscellaneous		48

* Contains sulphydryl compounds itself or after decomposition.

plot analysis to investigate characteristics of them in our laboratory. They showed the same characteristics as those shown previously [2]. Molecular typing of the DRB1 gene studied in 12 among 17 patients with alpha lipoic acid-IAS revealed DRB1*0406 in 10, DRB1*0403 in two patients, whereas all 11 patients with methimazole-IAS possessed DRB1*0406. Rapidly increasing numbers of cases with alpha lipoic acid-induced IAS have been confirmed to be reported since 2003.

Generally in Japan, alpha lipoic acid has gained popularity as a supplement for dieting and anti-aging since 2004. Formerly, it was used as a remedy for diabetic neuropathy in the western countries while it was prescribed for the cases of subacute necrotizing encephalopathy, hearing impairment, and Reye's syndrome in Japan. Alpha lipoic acid is a coenzyme of an enzyme which activates oxidative decarboxylation against pyruvic acid and alpha-keto acid in mitochondria. When it is taken orally, it is reduced to dihydrolipoic acid with sulphydryl componds in the presence of NADH or NADPH, having a strong reducing ability to protect peripheral cells from oxidative stress.

We previously reported that Graves' disease patients who carry DRB1*0406 developed IAS when they took methimazole (Odds ratio, 2727; $p < 1 \times 10^{-10}$) [8]. Matsushita, et al. indicated that a reducing compound such as methimazole may cleave the disulfide bond in vivo and allow DRalfa-DRB1*0406 complex on antigen-presenting cells to bind much of the linear fragment of insulin A chain, which may lead to the activation of self-insulin-specific T-helper cells [9].

Although the development of IAS is convinced to be more frequent in Japanese than Caucasians with respect to the evolution of HLA-DR4 alleles [10], it is conceivable that those who carry DRB1*0403 or DRB1*0407 which are more frequent in Caucasians could develop IAS when they take drugs such as alpha lipoic acid even though DRB1*0406 (Odds ratio, 56.6) is stronger predisposition to risk of development of IAS than DRB1*0403(Odds ratio, 1.6), and DRB1*0407 (Odds ratio, 1.1) [2].

Conflict of interest

There are no conflicts of interest.

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薬剤性インスリン自己免疫症候群

内　潟　安　子*

はじめに

インスリン治療中の糖尿病患者の意識障害の最も頻度の高いものは，もちろん低血糖症である．これはインスリン治療による低血糖症で，自発性低血糖とはいわない．自発性低血糖とは，主に空腹時におこりやすい原因不明で発症する低血糖をいう．

これから述べるインスリン自己免疫症候群は自発性低血糖症のひとつである．

1 低血糖症の分類

表1は成因別による低血糖症の分類である．内因性低血糖のなかに，食後特に次ぎの食事前に発症する反応性低血糖と，自発性低血糖がある．反応性低血糖は食事をしなければ発症しないものである．

自発性低血糖は主に空腹時におこる低血糖で，食事をきっかけにおこるといった低血糖症ではない．

自発性低血糖症をおこす疾患として反応性低血糖，インスリン受容体抗体による低血糖，インスリン自己免疫症候群，インスリノーマ，膵外腫瘍による低血糖などがあげられる．

表2に日本における自発性低血糖症の上位3つを示す[1]．これは2度の全国調査による結果であるが，第1位はインスリノーマで，第2位が膵外腫瘍による低血糖症，第3位がインスリン自己免疫症候群であった．

表1　成因による低血糖症の分類

- ●内因性低血糖
  - ★空腹時低血糖（自発性低血糖）
  - ★反応性低血糖（食後低血糖）
- ●誘発性低血糖
- ●外因性低血糖

表2　自発性低血糖（内因性空腹時低血糖）の原因の上位3つ

❶インスリノーマ
❷膵外腫瘍による
（non-islet-cell tumor hypoglycemia ; NICTH）
❸インスリン自己免疫症候群

2 インスリン自己免疫症候群の概念

インスリン自己免疫症候群は，これまでの症例を詳細に検討した結果，平田[2]は，①インスリン注射歴のないにもかかわらず重症の低血糖発作で発見される，②患者血中には大量のインスリン（IRI）が存在する，③その大部分はインスリン自己抗体と結合していると概念づけることができると述べた．

その後，インスリン自己免疫症候群は特定の

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Yasuko Uchigata : Drug-induced Insulin Autoimmune Syndrome.
Diabetes Center, Tokyo Wemen's Medical University School of Medicine.

HLAと強く相関することが明らかになった[3]．そこで，④インスリン自己免疫症候群患者のHLA-DR4（DRB1*0406）との強い相関を付け加える．今日までのところ，特定のHLA型と非常に強い相関を示す4疾患が報告されている．ankylosing spondylitis患者の88％はHLAB27[4]を，pemphigus vulgaris患者91％はDR4[5]を，narcolepsy患者のほぼ100％近くはDR2[6]を，primary sclerosing cholangitisのほぼ100％近くはHLA-DR Ⅲ52aをもつ[7]と報告された．インスリン自己免疫症候群は特定のHLAとの強い相関をもつ5番目の疾患となる．

3 DRB1*0406のインスリン自己免疫症候群に対する疾患感受性

過去に報告があった主治医をさがして患者の同意を得て全国から集めることのできたものと当方に直接依頼されたものを集めて，ポリクローナルインスリン自己抗体を産生した日本人インスリン自己免疫症候群50名のHLA型を調べることができた[8]．あとで述べるが，モノクローナルインスリン自己抗体を産生するインスリン自己免疫症候群は，HLAに関しては別のルールに従う．

その結果，ポリクローナルインスリン自己抗体産生インスリン自己免疫症候群にはBw62/Cw4/DR4のハプロタイプを持つものが多く，そのうちDR4の頻度が最も高いことがわかった．連鎖不平衡がDQ座はもちろんのこと，D座からC座，B座まで伸びることがわかる．また，2名はDR9/-を持っていた（オッズ比0.8（95％CI 0.39-1.82））．

DR4のgenotypeを調べると，DRB1*0403，DRB1*0406，DRB1*0407をもつことがわかった．インスリン自己免疫症候群を発症していない日本人をコントロール群として比較すると，DRB1*0406の発現頻度だけが56.6（95％CI 20.4-156）というオッズ比で，あとの2つのタイプはオッズ比は1.1（95％CI 0.09-12.0）ないし1.6（95％CI 0.47-5.22）であった（**表3**）．

このことは，DRB1*0406はインスリン自己免疫症候群に対する疾患感受性をもつといえるが，DRB1*0403ないしDRB1*0407，DR9は，たまたまインスリン自己免疫症候群を発症することがあるが，特にHLAが発症のし易さを後押ししているわけではない，という解釈になる．

インスリン自己免疫症候群の第1例は九州在の方で，平田幸正が九州大学に赴任中に発見した[9]．

表3 Incidence of DRB1 alleles, Glu^{74} in DR β1-chain and DBQ1 alleles in Japanese IAS polyclonal responders and control subjects

	IAS patients	Control	OR (95% confidence interval)	DRB1 chain amino acid residue		
				37	74	86
n	50	106	—	—	—	—
DRB1 allele						
DR4	48 (96)	40 (38)	39.6 (9.12～171)	—	—	—
DR9	12 (24)	29 (27)	0.8 (0.39～1.82)	Asn	Glu	Gly
DRB1*0406	42 (84)	9 (8)	56.6 (20.4～156)	Ser	Glu	Val
DRB1*0403	5 (10)	7 (7)	1.6 (0.47～5.22)	Tyr	Glu	Val
DRB1*0407	1 (2)	2 (2)	1.1 (0.09～12.0)	Tyr	Glu	Gly
Glu^{74} in β-chain	50 (100)	70 (66)	52.3 (6.95～393)	—	—	—
DQB1 allele						
DQA1*0301	50 (100)	74 (70)	44.1 (5.84～332)	—	—	—
DQB1*0302	48 (96)	26 (25)	73.8 (16.8～325)	—	—	—
DQA1*0301/DQB1*0302	48 (96)	23 (22)	86.6 (18.8～380)	—	—	—

Data are *n* (%) or OR(95% confidence interval).

その後もあとで述べるように，日本人には1年に数人の報告がなされる頻度であるが，海外からの報告はそれに比べ圧倒的に少ない[8]．

DRB1*0406というDR4 genotypeはもともと極東アジア人に多い，日本人に多いことは知られていた．そこで，なぜ海外からのインスリン自己免疫症候群の報告が少ないのかの疑問に答えるべく，東京大学人類遺伝学教室とタイアップして調査し，報告した[9]．

わかったことは，DRB1*0403は全世界に広く分布しているが，DRB1*0406は中国の北部から韓国，日本に分布，DRB1*0407は中米アメリカ大陸とポルトガルあたりに分布していた．そのことから，DRB1*0403からDRB1*0406とDRB1*0407が分かれて進化したものであろう，DRB1*0406は特に東アジアで進化し分布することになったと考えられた[10]．

4 日本人インスリン自己免疫症候群患者数

1970年より1993年末までに全国および地方の内科学会，内分泌学会，糖尿病学会で報告された症例，および1982年と1988年の全国2094の病院にお願いしたアンケート調査[1]，さらに当方へ個人的に報告された症例を合わせるとその数は212名にのぼった（**表4**）[11]．発症年齢は比較的高く60～69歳にピークを示した．男女差は全体的にははっきりしなかったが，20～29歳の女性が同年代の男性に比べ多かった．これはこの年代層の本症候群女性にバセドウ病を合併していることが多いことによると思われる．

2002年末までの報告を数えると269名になった[12]．医学中央雑誌データベースの報告も合わせ，2003年には274名にのぼった[13]．

2003年のつづきから医学中央雑誌データベースからひろうと，56例が追加された．

5 誘発薬剤の存在性

以前よりバセドウ病でメルカゾール服用中の症例に低血糖症状が出現することが報告され[14]，メルカゾールとの因果関係が注目されていた．

1970年より1993年末までの調査からの212例について発症時に使用されていた薬剤をまとめたものが**表5**である[15]．バセドウ病のためにメチマゾール（メルカゾール®）を，肝疾患，白内障，皮膚炎や関節リウマチのためにチオプロニン（チオラ®）を服用していた．7人はジンマシンの為にグルタチオン（タチオン®）を服用中に低血糖症状が出現した．これらの薬剤はいずれもSH基を含む薬剤である．

その他の薬剤には，トルブタマイド，ステロイド，ゴールドチオグルコース，カプトプリル，ペニシラミン，抗癌剤のアセグラトン，インターフェロンα[8]，加えて，βラクタム系ペニシリンG[16]，βラクタム系イムペナム[17]，ロキソプロ

表4 日本人インスリン自己免疫症候群212例の性別，年齢別低血糖症発症年齢

低血糖症発症年齢	男	女	計
0～ 9	0	1	1
10～19	1	1	2
20～29	4	13	17
30～39	10	7	17
40～49	20	18	38
50～59	24	19	43
60～69	25	25	50
70～79	20	15	35
80～89	3	6	9
合計	107	105	212

表5 インスリン自己免疫症候群診断時に存在した他の疾患と服用していた薬剤

薬剤	疾患	症例数
メチマゾール	バセドウ病	44
チオプロニン	慢性肝疾患	25
〃	白内障	6
〃	皮膚疾患	5
〃	関節リウマチ	2
グルタチオン	ジンマシン	7
その他の薬剤		35

フェン[18,19]，ピリチノール[20]，イソニアチッド[21]，ヒドララジン[22]が，これまでの報告の中から抽出されており，SH基との関連が言及できる可能性をもつものが多い（表6）．

2003年に，はじめてα—リポ酸により誘発されたと考えられるインスリン自己免疫症候群が報告されている[23]が，著者はその他の薬剤のひとつだろうと，ことの重大さを認識していなかった（図1）．

6 新たな薬剤の登場—α—リポ酸の重大性

2004年から2007年9月までの医学中央雑誌データベースから，56名のインスリン自己免疫症候群と診断されうる症例が抽出できる．なお，1型糖尿病発症時に同時にインスリン抗体をもつ症例はのぞいた．

表6　その他の薬剤の一覧

トルブタマイド
ステロイド
ゴールドチオグルコース*
カプトリル*
ペニシラミン*
アセグラトン
インターフェロンα
βラクタム系イムペナム*
ロキソプロフェン
ピリチノール*
イソニアチッド
ヒドララジン
α—リポ酸*

*SH基をもつものないし，分解後に関するもの

56名のうち，関連薬剤として，メルカゾールが11名，チオラが1名，ロキソプロフェン1名，にんにく（s—s結合を有するs—アリルメルカプトシステイン含有）疑い1名に，α—リポ酸が17名であった（表8）．2003年以降になって，急にα—リポ酸と関連したインスリン自己免疫症候群が増加してきたといえる（図2）．

7 メルカゾール服用中にインスリン自己免疫症候群を発症したバセドウ病患者のHLA型

上記に述べたように，インスリン自己免疫症候群を発症したバセドウ病患者は，いずれもメチマゾール（メルカゾール®）を服用していた．プロピルチオウラシル（チウラジール®）を服用していたバセドウ病患者はいなかった．メチマゾールはSH基をもつがプロピルチオウラシルはもたない．

メルカゾール®服用中にインスリン自己免疫症候群を発症したバセドウ病患者と服用中にもかかわらずインスリン自己免疫症候群を発症していないバセドウ病患者のHLA型を比較調査したことがある[24]．

表7にあるように，DR4を保有する率は，インスリン自己免疫症候群発症バセドウ病患者が100％である一方，インスリン自己免疫症候群未発症バセドウ病患者は36％とほぼ一般人口のそれと同じであった（$p<4\times10^{-5}$）．さらにDRB1*0406保持はオッズ比が2,727倍となった（$p<1\times10^{-10}$）．このことから，もしバセドウ病患者がDRB1*0406

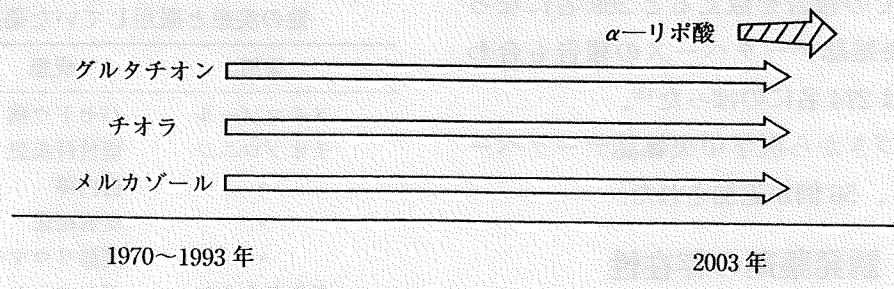


図1　代表的な関連する薬剤の出現（概念図）

保持して治療薬としてメルカゾール®を服用すれば，かならずインスリン自己免疫症候群を発症することが伺える．

8 強力な還元剤α—リポ酸の台頭

おおよそ2004年頃から日本では，ダイエットとか，アンチエイジング用のサプリメントとしてα—リポ酸がもてはやされるようになってきた．それ以前にも欧米では糖尿病性神経障害の治療薬として，日本でも亜急性壊死性脳症とか聴力障害やライ症候群の治療薬として使用されていた．

α—リポ酸はもともと体内にある酵素で，ミトコンドリア内でピルビン酸やα—ケト酸に対する酸化的脱炭酸反応を誘導する酵素の補酵素である．経口的に摂取されると，NADHやNADPH存在下でジヒドロリポ酸に還元され，細胞から漏れてでたものは酸化的ストレスから周辺の細胞を防御する実は強力な還元作用をもつ．

表7 Allele frequencies of DR4 group in patients with Graves' disease who developed or did not insulin autoimmune syndrome

DR4 allele	Graves' with IAS (n=13)	Graves' without IAS (n=50)	Odds ratio (95% confidence interval)	*P*
04	13 (100)[a]	18 (36)[a]	47.4 (5.78～389)	$<4\times10^{-5}$
0401	0 (0)	0 (0)	3.74 (0.22～63.6)	1.0
0403	0 (0)	2 (4)	0.72 (0.06～7.45)	<0.47
0405	0 (0)	14 (28)	0.09 (0.01～0.77)	<0.034
0406	13 (100)	0 (0)	2,727 (160～46,400)	$<1\times10^{-10}$
0407	0 (0)	1 (2)	1.22 (0.10～14.4)	<0.61

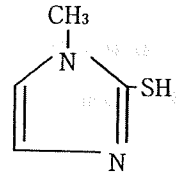
All 22 patients with IAS without Graves' disease also possessed DRB1*0406.
[a]The number of subjects is given, with the percentage in parentheses.

表8 α—リポ酸などが関係したと考えられるインスリン自己免疫症候群の一覧

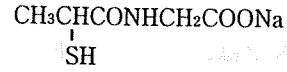
	著者名	症例年齢	性別	IRI μU/ml	%結合率	HLADRB1*	文献	報告県
1	橋永ら	55	女	8,149	95	406	糖尿病 46(2)：200, 2003	久留米
2	竹田ら	44	女	538	96	0406/0901	糖尿病 49(Supple 1)：S86, 2006＊	熊本
3	神谷ら	67	女	787	96	?	糖尿病 49(Supple 1)：S321, 2006	神奈川
4	西川ら	66	男	660	88	406	糖尿病 49(7)：587, 2006	東京
5	関本ら	30	女	著明高値	82	406	糖尿病 49(6)：478, 2006	神戸
6	吉岡ら	34	女	400	93	406#	日内分誌 82(3)：707, 2006	東京#
7	倉敷ら	64	女	126	93	DR4	日内分誌 82(4)：832, 2006	大阪
8	福留ら	34	女	高値	98.4	406	糖尿病 50(Supple 1)：S345, 2007	鹿児島
9	Takeuchi ら	55	男	2,531	93.3	406	Int Med 46(5)：237, 2007	松本
10	吉田ら	36	女	64.8	91	?	糖尿病 50(6)：457, 2007	大阪
11	佐々木ら	35	男	1,949	抗体陽性	406	糖尿病 50(7)：532, 2007	筑波
12	中島ら	34	女	518	95	406	糖尿病 50(8)：623, 2007	鹿児島
13	小河ら	36	女	995	82	?	糖尿病 50(10)：759, 2007	福岡
14	工藤ら	40	女	4,320	86	403	日臨検査自化会誌 32(4)：663, 2007	青森
15	松井ら	48	女	119.2	92	406	糖尿病 50(8)：641, 2007	富山
16	Yamada ら	45	女	13,240	81.2	403	Diabetes Care 30(12)：e131, 2007	仙台

#その後内潟が拝見して，DRB1*0406，α—リポ酸服用と関係することが判明
＊Furukawa N et al Diab Res Clin Prac 75：366, 2007と同じ

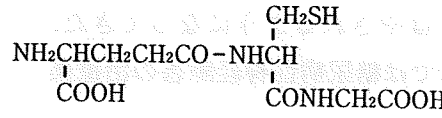
Methimazole



α-mercaptopropionyl glycine



glutathione



D-penicillamine

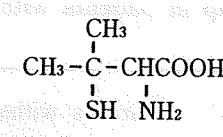
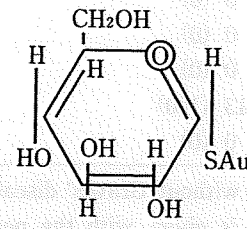
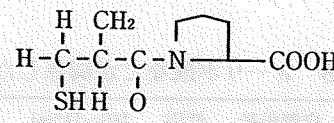


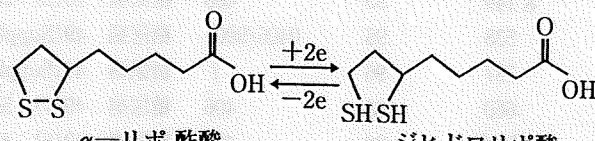
図 2-1　Sulfhydryl Compounds

gold thioglucose



captopril





α—リポ酸　　ジヒドロリポ酸

α—リポ酸とジヒドロリポ酸

図 2-2　Sulfhydryl Compounds

9 SH基とインスリン自己免疫症候群の発症メカニズム

DRB1*0406保有Tリンパ球に対するヒトインスリン添加後のTリンパ球の増殖[26]は，抗DR抗体では抑制されるが抗DQ抗体では抑制されないこと，DRB1*0405保有Tリンパ球に対してはヒトインスリン添加による増殖はおこらなかった[27]ことから，DQ分子よりDR分子にヒトインスリンフラグメントが抗原提示されると考えている．SH基がヒトインスリンを還元し，ヒトインスリン分子のcryptic selfを顕性化させることに

よって，自己抗原となるのではないかと予想される[28]．

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Reprinted from THE LANCET, *February 15, 1992, pp. 393–394*

Strong association of insulin autoimmune syndrome with HLA-DR4

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Insulin autoimmune syndrome is characterised by spontaneous hypoglycaemia without evidence of exogenous insulin administration, a high serum concentration of total immunoreactive insulin, and the presence of insulin autoantibodies in high titre. HLA typing of 27 patients with insulin autoimmune syndrome showed that all had DR4, which was present in only 43% of 51 healthy controls (odds ratio 72·1, $p < 2 \times 10^{-6}$), and 19 (70%) of the patients were positive for the allelic combination, Cw4, Bw62, and DR4. Analysis of the nucleotide sequences of the DRB1, DQA1, and DQB1 genes showed that all the patients had DRB1*0406, DQA1*0301, and DQB1*0302, compared with only 14% of the controls (odds ratio 281, $p < 1 \times 10^{-10}$). We conclude that the development of insulin autoimmune syndrome is associated with a strong genetic predisposition.

Lancet 1992; **339**: 393–94.

The combination of a high serum concentration of total immunoreactive insulin, the presence of insulin autoantibodies, and fasting hypoglycaemia is known as the insulin autoimmune syndrome. The disorder was first reported in Japan,[1] where it is commonest, but there have been cases in caucasians.[2] Although insulin autoantibodies are commonly found before or at onset of insulin-dependent diabetes mellitus (IDDM),[3] the titre of autoantibodies is generally higher in patients with insulin autoimmune syndrome than in those with IDDM. It is not yet clear whether insulin autoantibodies have the same characteristics in both disorders. We have previously reported HLA associations in insulin autoimmune syndrome obtained by questionnaire.[4] Class II antigens seem to be more strongly related to the disorder than are class I antigens.

Blood samples were collected from 27 patients (13 male, 14 female; aged 26–69 years) with insulin autoimmune syndrome by their primary physicians, at least 5 years after the resolution of hypoglycaemic attacks. All the patients had more than 100 mU/l immunoreactive insulin at disease onset (normal < 10 mU/l) and

more than 30% iodine-125-labelled insulin binding (compared with less than 5% in patients with newly diagnosed IDDM in this assay). Enzyme-linked immunosorbent assay showed the presence of human IgG antibodies against human insulin, which must be autoantibodies since there was no history of insulin injection. No patient had insulinoma; all have been healthy since resolution of the hypoglycaemic attacks. Pancreatic tumours were sought by computed tomography, ultrasonography, angiography, and pancreaticocholangiography in 6 patients, but none was found. 8 patients had received methimazole for Graves' disease; 9 mercaptopropionyl glycine (tiopronin) for liver dysfunction, cataract, or dermatitis; and 1 gold thioglucose for bronchial asthma. The hypoglycaemic attacks started about 1 month after drug administration. 51 healthy Japanese subjects served as controls. HLA typing was done by the standard microlymphocyte toxicity test in various laboratories; some results were confirmed in our laboratory. HLA specificities and alleles were described according to the Nomenclature for Factors of the HLA system, 1987 and 1990. The chi-square test, with Yates' correction when necessary, was used to assess statistical significance.

19 of the 27 patients had an allelic combination typical of Japanese people—Cw4, Bw62, and DR4 (table I).[5]† All 27 were positive for the DR4 antigen. The antigens Bw62, Cw4, and DR4 were significantly associated with the insulin autoimmune syndrome (table II), but DR4 showed the strongest association.

TABLE I—HLA TYPING OF PATIENTS WITH INSULIN AUTOIMMUNE SYNDROME

Patient	HLA				
	A	B	C	DR	DQ
1	2, 26	40, w46	w4, –	4, –	NT
2	11, 33	44, w62	w4, –	4, w13	w1, w3
3	11, 24	44, w62	w4, –	4, 9	NT
4	24, –	w52, w62	w1, w3	4, w6	NT
5	11, 24	w62, –	w4, –	4, –	w3, –
6	11, 24	w60, w62	w4, –	4, 9	NT
7	11, –	54, w62	w1, w4	4, w8	w1, w3
8	11, 33	44, w62	w4, –	4, 9	w3, –
9	11, 31	16, w62	w4, w7	2, 4	NT
10	24, 26	35, w61	w3, –	4, 9	NT
11	24, 26	w62, –	w3, w4	2, 4	NT
12	24, 26	w62, –	w4, –	4, –	NT
13	24, w33	17, w62	w3, w4	4, w6	w1, w3
14	2, 11	w61, w62	w4, –	4, 9	w3, –
15	26, –	35, –	w3, –	4, w8	w3, –
16	24, –	54, w62	w1, w4	4, –	w3, –
17	2, 33	44, 35	w3, –	4, w13	NT
18	11, 24	w61, w62	w4, –	4, w12	w3, w7
19	24, 31	w62, –	w3, –	4, w12	w3, w7
20	2, 11	51, w62	w4, –	4, –	w3, –
21	2, –	w46, –	w11, –	4, w8	w1, w3
22	2, 24	15, 35	w3, –	4, 9	w3, –
23	2, 26	35, w62	w4, –	4, w12	NT
24	24, 26	35, w62	w3, w4	2, 4	w1, w3
25	2, 11	w60, w62	w3, w4	4, –	NT
26	2, 11	w55, w62	w1, w3	4, w6	w1, w3
27	11, –	w62, –	w1, w3	4, 9	NT

NT = not tested

† Tables showing full details of patients, primers and probes used, and frequencies of other alleles available from *The Lancet*.

TABLE II—PHENOTYPE FREQUENCIES OF HLA ANTIGENS IN PATIENTS WITH INSULIN AUTOIMMUNE SYNDROME (IAS)

Antigen	No present in:		Odds ratio	p
	Controls (n=51)	IAS patients (n=27)		
A11	15	12	1·90	<0·1
A24	19	13	1·60	<0·3
B35	10	6	1·20	<0·7
B62	13	22	12·9	$<2\times10^{-5}$
Cw4	8	18	10·8	$<5\times10^{-6}$
DR1	5	0	∞	<0·2
DR2	17	3	0·25	<0·6
DR4	22	27	72·1	$<2\times10^{-6}$
DRw6/w13/w14	7	5	1·48	<0·5
DR7	1	0	∞	1·0
DRw8	13	3	0·37	<0·2
DR9	13	7	1·00	<0·9
DRw12	6	3	0·94	1·0

We analysed the nucleotide sequences of HLA class II genes by the polymerase chain reaction sequence-specific oligonucleotide chemiluminescent method.[6]† DR4 group-specific amplification was done. All 27 patients had the DRB1*0406 allele compared with only 7 of the 51 controls. The allele was positive for DRB37-1, DRB70-3, and DRB86-3, and negative for DRB57-1, DRB70-1, DRB70-5, and DRB86-1. In addition, all the patients had DQA1*0301 and DQB1*0302.† Since the frequency of the allele combination DRB1*0406/DQA1*0301/DQB1*0302 in the 51 controls was 14%, this difference was highly significant (odds ratio 281, $p < 10^{-10}$). The frequencies of the other HLA-DR4 specificities were lower than in controls, but the differences did not achieve significance in this study.

Insulin autoimmune syndrome is the latest of very few disorders for which all affected patients have the same HLA antigens. Since there is a strong linkage disequilibrium between DRB1*0406, DQA1*0301, and DQB1*0302 in Japanese people it is difficult to find out which allele is most closely linked to the development of insulin autoimmune syndrome.

Ziegler and colleagues[7] reported that among patients with type 1 diabetes and their relatives, those positive for DR4 had a higher prevalence of insulin autoantibodies than did those without DR4. However, no strong association between HLA type and the concentration of insulin autoantibodies was reported. Type 1 diabetes did not develop in any patients in our study.

There have been 190 reported cases of insulin autoimmune syndrome during the past 20 years in Japan, compared with only about 20 in Europe,[8] this difference suggests an effect of race in the development of the disorder. It is noteworthy that HLA-DRB1*0406 has a high prevalence in Korean and Japanese people (unpublished).

More than half the patients in this study and about a third of patients with insulin autoimmune syndrome from other countries had previously received methimazole, mercaptopropionyl glycine, gold thioglucose, glutathione,

or D-penicillamine;[8,9] all these drugs are sulphydryl compounds. 1 of our patients had her first hypoglycaemic attack 2 days after the administration of tolbutamide, a sulphonyl-urea compound. Further studies on the relations among insulin autoimmune syndrome, HLA-DRB1*0406/DQA1*0301/DQB1*0302, and such drugs may shed further light on the pathogenesis.

We thank Dr M. Hakamata, Dr A. Takagi, Dr Y. Akamine, Dr T. Sugimoto, Dr H. Kurahachi, Dr T. Nishi, Dr C. Sugimoto, Dr Y. Oka, Dr I. Morimoto, Dr H. Hara, Dr K. Nogi, Dr K. Yamashita, Dr T. Kuzuya, Dr H. Koushima, Dr T. Hashimoto, Dr J. Suzuki, Dr K. Ishida, Dr T. Murakami, Dr K. Tanaka, Dr M. Chino, Dr J. Yamakawa, Dr H. Hayashi, Dr N. Sano, and Dr S. Yokosawa, who kindly provided blood samples; Miss Masami Yanagisawa for technical assistance; and Mrs Noriko Doi for preparing the paper.

Please notify us (fax: 81–3–3358–1941) of patients who present with a high titre of insulin autoantibody.

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Printed in Great Britain by Robquest Ashford Kent

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Differential Immunogenetic Determinants of Polyclonal Insulin Autoimmune Syndrome (Hirata's Disease) and Monoclonal Insulin Autoimmune Syndrome

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The insulin autoimmune syndrome (IAS), or Hirata's disease, is characterized by the combination of fasting hypoglycemia, high concentration of total serum immunoreactive insulin, and presence of autoantibodies to native human insulin in serum. Autoantibody production is classified as monoclonal or polyclonal, with the majority of IAS cases classified as polyclonal. Previously, we observed a striking association between the human leukocyte antigen (HLA) class II alleles DRB1*0406/DQA1*0301/DQB1*0302 and Japanese IAS patients with polyclonal insulin autoantibodies (IAAs) and T-cell recognition of human insulin in the context of DRB1*0406 molecules. Because of such a strong HLA association in IAS, we performed intra- and interethnic studies on IAS-associated DRB1 alleles and searched for the critical amino acid residue(s) for IAS pathogenesis. Glutamate at position 74 in the HLA-DR4 β1-chain was presumed to be essential to the production of polyclonal IAA in IAS, whereas alanine at the same position of the HLA-DR β1-chain might be important in the production of monoclonal IAA. *Diabetes* 44:1227–1232, 1995

Human leukocyte antigen (HLA) is implicated in the genetic background of susceptibility to a number of diseases. Some of the diseases are related to specific amino acids on certain domains of HLA class II molecules that are distal to cell membranes (1–4). However, there has not been enough evidence that such amino acids on HLA class II molecules are essential for self-peptide presentation to T-cells in autoimmune diseases.

Our recent studies indicated that all the insulin autoimmune syndrome (IAS) patients had specific HLA class II alleles, DRB1*0406, DQA1*0301, and DQB1*0302, which allowed T-cells to proliferate when autologous antigen-presenting cells were exposed to human insulin (5,6). Further study indicated that gene products of DRB1*0406 act as the dominant restriction element for the presentation of human insulin (7). To our knowledge, IAS is the only autoimmune disease in humans where the target antigen (insulin) and the presenting molecule (HLA-DRB1) have been clearly elucidated.

There have been 197 reported cases of IAS during the past 20 years in Japan (8), compared with only about 20 cases in Caucasians (9,10) in the almost 25 years since Hirata et al. (11) first described the disease in 1970. This difference suggests an ethnic difference in the distribution of the susceptibility gene(s) to IAS. It is noteworthy that DRB1*0406 has a high prevalence in healthy Japanese and Koreans, whereas the allele is rare in Caucasians (12). The critical amino acid residues(s) of DRB1*0406 for IAS pathogenesis may be determined by the search for alleles other than DRB1*0406 associated with the development of IAS in extended studies in Japanese and other human populations.

In the present study, IAS-associated HLA-DRB1 alleles were examined in terms of clonality of insulin autoantibodies (IAAs) and intra- and interethnic differences to determine the HLA risk for IAS in patients from different countries with either polyclonal or monoclonal insulin autoantibodies. Of the 197 IAS patients in Japan registered in our records (8), approximately one-fourth were subjected to serological HLA typing and further DNA-based allele typing in this study.

RESEARCH DESIGN AND METHODS

IAS patients. IAS, or Hirata's disease, is characterized by the combination of fasting hypoglycemia, high concentration of total serum immunoreactive insulin, and presence of autoantibodies to native human insulin (IAAs) (13). In addition to our previously described 32 Japanese, 2 Korean (14), and 1 Chinese patient (15), a further 19 Japanese and 6 Caucasian IAS patients were examined in the present study (Japanese patients 33 to 50 and the white American patient [16,17] in Table 1, and 1 Japanese, 1 Norwegian [18,19], 1 Swiss [20], and 3 Italian patients [21–23] in Table 2). IAS development was associated with drug exposure in 36 of the 60 (62%) patients. In 30 of these 36 (83%) patients, the associated drug was a sulfhydryl compound: methimazole, carbimazole, glutathione, penicillamine, or α-mercaptopropionyl glycine (Tables 1 and 2) (24,25). Blood samples from the patients were provided by their primary physicians.

Determination of features of IAAs. IAAs from IAS patients were classified as polyclonal or monoclonal on the basis of affinity curves for

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Received for publication 21 November 1994 and accepted in revised form 20 June 1995.

HLA, human leukocyte antigen; IAA, insulin autoantibody; IAS, insulin autoimmune syndrome; OR, odds ratio; PCR, polymerase chain reaction.

TABLE 1
Summary of clinical characteristics of IAS polyclonal responders at onset of IAS

Ethnic background	Patient no.	Age (years)	Sex	T-IRI (pmol/l × 10^3)	^{125}I-insulin binding (%)	Drug	Associated disease	HLA-DR
Japanese	1	26	F	114.3	69	MTZ	Graves'	4, —
Japanese	2	52	F	54.5	73	GTG	Bronchial asthma	4, 13
Japanese	3	47	M	23.4	79	—	—	4, 9
Japanese	4	58	M	0.8	48	—	—	4, —
Japanese	5	54	F	60.0	70	MTZ	Graves'	4, —
Japanese	6	36	M	8.2	59	—	—	4, 9
Japanese	7	45	F	7.2	32	MTZ	Graves' Hashimoto's IgA nephropathy	4, 8
Japanese	8	62	M	12.6	69	—	—	4, 9
Japanese	9	54	M	4.4	81	MPG	Liver dysfunction	2, 4
Japanese	10	61	F	5.1	72	MPG	Cataract	4, 9
Japanese	11	44	M	3.0	70	MPG	Dermatitis	2, 4
Japanese	12	39	F	2.7	69	MTZ	Graves'	4, —
Japanese	13	69	M	12.3	65	—	—	4, 6
Japanese	14	57	F	2.8	51	—	—	4, 9
Japanese	15	68	F	11.7	68	MPG	Liver dysfunction	4, 8
Japanese	16	48	M	11.1	81	MTZ	Graves' Drug-induced arthritis	4, —
Japanese	17	64	M	4.6	82	MPG	Dermatitis	4, 13
Japanese	18	58	F	12.0	81	—	—	4, 12
Japanese	19	49	M	11.9	48	MPG	Liver dysfunction	4, 12
Japanese	20	69	F	167.2	67	TBM	NIDDM	4, —
Japanese	21	55	M	0.9	48	MPG	Liver dysfunction	4, 8
Japanese	22	53	F	35.0	55	—	—	4, 9
Japanese	23	69	M	47.0	65	MTZ	Graves'	4, 8
Japanese	24	36	F	192.5	79	MTZ	Graves'	2, 4
Japanese	25	43	F	23.0	57	MTZ	Graves'	4, —
Japanese	26	68	M	5.4	64	MPG	Liver dysfunction	4, 6
Japanese	27	66	F	21.0	57	MPG	Cataract	4, 9
Japanese	28	49	F	18.0	83	MTZ	Graves'	4, —
Japanese	29	54	M	3.4	67	MPG	Liver dysfunction	4, —
Japanese	30	70	F	46.8	94	MTZ	Graves'	4, —
Japanese	31	67	F	120.0	80	—	—	4, 8
Japanese	32	50	F	1.7	64	GTT	Urticaria	1, 4
Japanese	33	52	M	13.3	38	—	—	④6 0403
Japanese	34	74	M	5.2	78	—	—	4, —
Japanese	35	54	M	3.0	76	—	—	4, 8
Japanese	36	79	M	3.1	70	—	—	2,④0403
Japanese	37	49	F	1.4	88	—	NIDDM	4,9 0407
Japanese	38	59	M	24.3	69	MPG	Liver dysfunction	4, 8
Japanese	39	66	M	6.2	91	—	Hypertension	4, —
Japanese	40	84	F	5.0	73	MPG	Liver dysfunction	4, 6
Japanese	41	42	F	2.5	24	MPG	Liver dysfunction	4, 9
Japanese	42	71	F	5.1	67	—	—	4, 15
Japanese	43	70	F	4.5	84	INF-α	Renal cell carcinoma	4, 8
Japanese	44	65	M	1.1	50	—	—	4, 8
Japanese	45	64	M	9.3	48	Steroid	Polymyositis	9, —
Japanese	46	49	F	5.4	75	—	—	2, 4
Japanese	47	71	M	3.0	68	MPG	Liver cirrhosis	4, 12
Japanese	48	81	M	1.4	92	—	—	4, 14
Japanese	49	77	M	0.7	64	Aceglatone	Urinary bladder carcinoma	9, —
Japanese	50	71	F	7.4	80	AHT drugs	Hypertension	4, 6
Korean	1	61	F	12.0	90	MTZ	Graves'	4, —
Korean	2	31	F	8.9	62	MTZ	Graves'	4, 9
Chinese	1	18	F	36.4	82	MTZ	Graves'	4, —
White American	1	61	F	4.8	1:64*	PNC	Rheumatoid arthritis	4, 5

Hypoglycemic attacks occurred ~6 weeks after drug administration. All of the patients have remained healthy since the resolution of the hypoglycemic attacks (21). Abdominal computed tomography, abdominal ultrasound, abdominal angiography, and pancreaticocholangiography examinations performed in six patients failed to reveal the presence of a pancreatic tumor. Total immunoreactive insulin (T-IRI) (normal range, <5 μU/ml) (6) and ^{125}I-labeled human insulin binding (normal range, <5%) (6) were measured as previously described. Methimazole (MTZ) was administered orally for treatment of Graves' disease. Gold thioglucose (GTG) was administered intramuscularly for treatment of bronchial asthma. α-mercaptopropionyl glycine (MPG) was administered orally for treatment of liver dysfunction, cataracts, or dermatitis. Only one tablet (50 mg) of tolbutamide (TBM) was administered orally for treatment of non-insulin dependent diabetes (NIDDM) before the hypoglycemic attack. Glutathione (GTT) was administered intravenously for treatment of urticaria. Interferon-α (IFN-α) was administered intravenously for treatment of renal cell carcinoma (37). The anticancer drug aceglatone was administered orally for treatment of urinary bladder carcinoma. Japanese patient 50 was taking antihypertensive (AHT) drugs when IAS developed. Penicillamine (PNC) was administered orally for treatment of rheumatoid arthritis. Japanese patients 33, 36, 42, 46, and 48 possessed the DRB1*0403 allele. Japanese patient 37 and the white American patient possessed the DRB1*0407 allele. The remaining patients, with the exception of Japanese patients 45 and 49 (DR9 homozygotes), possessed the DRB1*0406 allele. *1:64 was expressed as positive (9,10).