本研究は厚生労働省科学研究における多施設共同研究である。本研究に関する問い合わせは本研究事務局の、東京女子医科大学糖尿病センター内潟安子である。

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自発性低血糖全国実態調査委員会

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当院は、

平成21年度厚生労働省科学研究
「自発性低血糖症の全国調査」

に参加しています。

自発性低血糖症とは、原因なく低血糖をおこす病気で、全国にどれくらいの方が低血糖をおこしているのか、なにか原因になるものがないか、そのようなことを調査しています。

個人情報には十分に注意しておこなっておりますことをお伝えします。

平成21年８月

自発性低血糖症の実態把握のための全国調査
説 明 文 書

1．はじめに

厚生労働省の厚生労働科学研究事業のひとつとして、私たちは、原因なく低血糖をおこしてしまった皆さんの全国調査をおこなっています。

これまでに、第1回は1982年、第2回は1988年に、東京女子医科大学糖尿病センター独自に自然に発症した低血糖症の全国調査を行ない、この調査結果により、はじめて日本における低血糖原因疾患の順位が明らかになりました。上位3疾患はインスリノーマという病気と、膵外腫瘍という病気と、インスリン自己免疫症候群でありました。そして、低血糖症になる皆さんの一部に、SH 基というものをもつ薬物を服用している方がいらっしゃることも明らかになり、とても学術的に大事な結果が得られました。

最近、サプリメントを摂取後に低血糖になることが散見されます。そこで、いま日本人にどれくらいの低血糖の方がいるのか、薬物やサプリメントが関連しているのか、これらを調査しようと企画しました。厚生労働省も支援してくださっていますので、ご協力、よろしくお願い申し上げます。

2．調査の対象

原因なく低血糖をおこした患者さんで、調査への協力の同意をいただくことのできた方。

3．調査の方法および内容

同意をいただけましたら、次ぎのことがらについて、主治医の先生にお聞きしたいと思います。

(1) 年齢　性別
(2) 低血糖症の前駆症状の期間
(3) 発症時服用薬物や嗜好品、サプリメントなどの有無と種類
(4) 胃切の有無
(5) 低血糖発症時間帯、昏睡の有無
(6) 予後（自然寛解の有無、再発の有無）
(7) 薬物治療の有無
(8) 血糖値などの検査値
(9) HLA タイプおよびアリールの検査

4．調査承諾後の利益と不利益について

本研究の結果があなた個人にすぐに有益な情報をもたらす可能性は低いと考えられます。しかし，この研究によって解明された成果を社会に還元することにより、将来、病気のリスク診断や予防、治療などがより効果的に行われるようになる可能性があります。

また、個人情報は厳密に管理されますが、万が一外部に漏れた場合プライバシーの侵害などにつながる可能性が考えられます。

5. 個人情報の保護

そこで、カルテから得られたデータには、すぐ新たに符号をつけます。主治医や調査解析をおこなうものにとって誰のものかわからなくなるように、前項のデータの分析および解析は、新しくつけた符号のもとにおこないます。これを「二重連結可能匿名化」とよびます。(名前など個人を識別できるものを除いた状態で、分析をおこなう研究者に渡されます)。こうすると、あなたの分析結果は、分析をおこなう研究者にとって、誰のものかは全くわからなくなります。

ご不明な点がございましたら、遠慮なく担当医にお尋ねください。

6. 同意の任意性

同意をいただいた後でも、研究に協力することが困難と感じましたら、協力の撤回はいつでもできます。また、協力するしないは、あなたの自由意志に任されておりますので、いかなる理由でも強制されるものではありません。もちろん、同意をいただけなくても、あなたの不利益になることは一切ありません。

7. 調査結果の公表

あなたの協力によって得られた結果は、学会や学術雑誌で、公に発表されることがあります。ただし、あなた個人を特定する情報（氏名、住所、カルテ番号など）が公表されることは一切ありません。

8. 調査から生じる知的所有権について

研究の結果として特許などの知的所有権が生じる可能性がありますが、その権利は研究者に属し、調査承諾されたあなたには属しません。

9. 費用負担に関する事項

ここで行われる研究に必要な費用は、あなたが負担することはありません。しかし、この研究によって、新しい検査や治療が必要となったときや、本来必要な検査・治療には一般診療と同様の個人負担が必要となります。

10. カウンセリング

あなたが病気のことやこの研究に関して不安に思うことや相談したいことがある場合は、カウンセリングをうけることができます。

<u>自発性低血糖全国実態調査委員会</u>

岩本安彦（代表）東京女子医科大学糖尿病センター

田嶋尚子（東京慈恵会医科大学）、西村理明（東京慈恵会医科大学）吉岡成人（北海道大学）、伊藤光泰（藤田保健衛生大学）、花房俊昭（大阪医科大学）、荒木栄一（熊本大学）、

事務局　内潟安子（東京女子医科大学糖尿病センター）

平成21年7月13日

自発性低血糖症の実態把握のための全国調査用紙

ご記載の先生：医療機関名＿＿＿＿＿＿病（医）院（＿＿＿科）＿＿＿＿＿＿＿先生

記載年月日：2009/平成２１年＿＿月（西暦と平成＿年はどちらかをお書き下さい）

自発性低血糖症を発症した患者さん（貴院作成の匿名番号＿＿＿＿＿＿＿＿）

1. 診断名　1. インスリーマ　2. 腫瘍（例：肝細胞がん：＿＿＿＿＿＿＿＿＿＿）　3. インスリン自己免疫症候群　4. その他（＿＿＿＿＿＿＿＿＿＿）（←以上のどれかに〇をつけて詳細を）

2. 発症時の年齢　＿＿歳　　性別　男・女　（←どちらかに〇を）

3. 体重［　.　］kg　身長［　.　］cm　腹囲［　.　］cm　血圧［　/　］mmHg

4. 発症年月日　＿＿年　＿＿月＿＿日ごろ

以下、わかる範囲で、ご記載をお願いします（上記診断に不要の項目もあります）。

5. 発症前に服用していた薬剤やサプリメント、嗜好品など

＿＿＿＿＿＿　＿＿＿＿＿＿　＿＿＿＿＿＿　＿＿＿＿＿＿

（書き切れない場合は裏面に記載をお願いします→）

6. 症状が出現して初診するまでの期間　＿＿＿＿＿＿くらい
7. 低血糖持続期間　＿＿＿＿＿＿くらい

（６．７とも、７日間くらい、１ヶ月くらい、１年くらいという具合にお願いします）

8. 低血糖のおこりやすい時間帯　＿＿＿＿＿＿（早朝、昼食前、夕食前、１日中　など）
9. 昏睡の有無　あり・なし（←どちらかに〇を）
10. 重症時の検査値についてお願いします。

上記測定時にもっとも近い時期の総IRI［　.　］μU/ml　遊離IRI［　.　］μU/ml

C−ペプチド［　・　］ng/ml　IGF-II［　　］ng/ml（基準値［　　］）

ブドウ糖負荷試験	前	３０分	６０分	９０分	１２０分	
血糖	＿＿	＿＿	＿＿	＿＿	＿＿	mg/dl
IRI	＿＿	＿＿	＿＿	＿＿	＿＿	μU/ml

^{125}Iインスリン結合率［　・　］%（正常値［　・　］%未満）

11. HLAタイプ　A＿＿/＿＿B＿＿/＿＿C＿＿/＿＿DR＿＿/＿＿DQ＿＿/＿＿

12. DR DNAタイプ（allele）DRB1＿＿/＿＿　DQA1＿＿/＿＿　DQB1＿＿/＿＿

（HLAのデータをコピーいただいてもけっこうです）

13. 胃切の有無　あり・なし（←どちらかに〇を）
14. 再発の有無　あり・なし（←どちらかに〇を）

＊ありの患者さんにつき、どれくらいの期間をおいて再発でしょうか。＿＿＿＿＿＿くらい

＊ なしの患者さんにつき、先生の知る限り、現在までどのくらいの期間、低血糖なしでしょうか。＿＿＿＿＿＿くらい

15. 上記以外の貴診断への確定に要した検査よび値＿＿＿＿＿＿＿＿＿＿＿＿

16. 学会、地方会、論文などに報告済みの場合は、コピーもご送付いただければ幸甚です。

学会名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿　＿＿＿＿年

雑誌名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿　＿＿＿巻・ページ数＿＿＿＿・＿＿＿＿年

III. 研究に使用した刊行物

本文にある文献番号順に記す

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ELSEVIER

Diabetes Research and Clinical Practice, 24 Suppl. (1994) S153–S157

DIABETES RESEARCH AND CLINICAL PRACTICE

Insulin autoimmune syndrome in Japan

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Abstract

Since 1970, 197 patients with insulin autoimmune syndrome (IAS) showing severe spontaneous hypoglycemia have been reported in Japan. This is characterized by a high titer of anti-insulin autoantibodies without evidence of exogenous insulin administration. IAS is the third leading cause of spontaneous hypoglycemia in Japan, while only 21 cases have been reported in Europe and the United States. High levels of the extractable native human insulin and of the characteristic insulin autoantibodies in the sera of the IAS patients have been proved. Recently a significant association of HLA-DRB1*0406/DQA1*0301/DQB1*0302 with this syndrome has been found in the IAS patients in Japan.

Keywords: Insulin autoimmune syndrome; Hypoglycemia; HLA-DRB1 gene

1. Introduction

When the first patient with spontaneous hypoglycemia associated with the production of insulin autoantibodies, so-called insulin autoimmune syndrome (IAS), was reported by Hirata et al. [1] in Japan in 1970, many questions were raised, its differential diagnosis from factitious hypoglycemia, the causes of this syndrome, the mechanisms to produce hypoglycemia in this syndrome and so on. Immediately after the first patient was diagnosed with IAS, several other patients were reported with the same syndrome over five years [2–5], and reports of a total of 197 patients in Japan from 1970 to 1992 have been registered. Besides the analysis of those reports, several studies concerning the causes of IAS and the hypoglycemia have been carried out by us.

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2. Insulin autoimmune syndrome as the third leading cause of spontaneous hypoglycemia in Japan

Takayama-Hasumi et al. [6] analyzed the results of questionnaires sent to 2094 large or general hospitals throughout Japan to investigate the causes of severe spontaneous hypoglycemic attacks from 1979 to 1981. The survey revealed three main causes for the hypoglycemic attacks: insulinoma, extrapancreatic neoplasms and IAS. The second survey carried out 6 years later from 1985 to 1987 gave the same results.

3. Onset age and sex distribution of 197 IAS patients reported in Japan from 1970 to 1992

The records of 197 patients with IAS reported from 1970 to 1992 were carefully examined [7]. Age of onset and sex distribution of the 197 patients are listed in Table 1. The peak age of onset was 60–69 years for both sexes.

SSDI 0168-8227(94)00910-M

Table 1
Age at onset and sex distribution in Japanese IAS patients, 1970–1992

Age at onset	IAS patients		
	Male (*n*)	Female (*n*)	Total
0–9	0	1	1
10–19	1	1	2
20–29	3	12	15
30–39	10	7	17
40–49	20	16	36
50–59	21	19	40
60–69	22	24	46
70–79	19	14	33
80–89	2	5	7
Total	98	99	197

IAS, insulin autoimmune syndrome.

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

4. Trigger of onset of IAS

In Japan, methimazole (MTZ) has been used for the treatment of Graves' disease and α-mercaptopropionyl glycine (MPG) for the treatment of chronic hepatitis, dermatitis, cataract and rheumatoid arthritis, and glutathion (GTT) for urticaria. These drugs containing the sulfhydryl (SH) group were found to play a role in triggering the development of IAS [4,8,9].

Among 197 patients with IAS, 44 had been treated with MTZ just before the first attack of hypoglycemia caused by IAS, 34 with MPG, 7 with GTT, and one with captopril [7]. There were 28 IAS patients who had received medication based on non-SH compounds just before the onset of IAS and 83 patients had no history of receiving any medicine just before the onset of IAS.

5. Clinical course and treatment in 197 patients with IAS

The duration of hypoglycemic attacks was relatively short. In 62 (31.5%) of the 197 patients the period lasted less than one month, and only 12 patients had a period of attack longer than one year. Spontaneous remission occurred in 162, while in the remaining 35 patients some specific treatments were introduced as shown in Table 2 [7]. Among these 35 patients 6 patients were misdiagnosed as having insulinoma, and this was followed by partial excision of the pancreas which was effective in reducing attacks. Hyperplasia of the islet B-cells of the excised part of the pancreas was reported in some IAS patients [1,2].

6. Insulin in the sera of the patients with IAS

The insulin in the sera of IAS patients was native human insulin itself [10]. Fig. 1 shows total extractable IRI and ^{125}I-insulin binding % of the sera of patients with IAS. The IRI levels during hypoglycemic attacks were quite enormous [4].

7. Insulin autoantibodies of IAS

The sera from 24 patients with IAS in Japan were tested by us to determine the immunoglobulin class, the subclass and the light chain types of insulin autoantibodies [11]. All insulin antibodies belonged to the IgG group. One patient seemed to have monoclonal antibodies such as an IgG_1 (lambda) single subclass [11] which had a very low affinity constant and a quite large binding capacity against human insulin in Scatchard

Table 2
Disease course and treatment in 197 Japanese IAS patients, 1970–1992

	IAS patients		
	Male (*n*)	Female (*n*)	Total
Spontaneous remission	84	78	162
Treatment			
Steroids	5	17	22
Pancreatic surgery	3	3	6
Plasmapheresis	5	0	5
Azathioprine	1	0	1
6-Mercaptopurine	0	1	1
Total	98	99	197

IAS, insulin autoimmune syndrome.

analysis [12]. Further studies concerning this particular serum sample were carried out by Uchigata et al. [13]. Scatchard analysis of the serum in another patient with IAS showed an obvious prozone phenomenon of antibodies to human insulin [14]. Besides those two patients mentioned above, even the high affinity site of the antibodies of IAS presented lower affinity constants and larger binding capacities than insulin antibodies produced by exogenous insulin injection in diabetic patients [14].

8. Strong association of IAS with HLA-DR4

Uchigata et al. [15] reported that serological typing of 27 patients with IAS showed that all of the patients had DR4, which was presented in 43% of the normal Japanese controls (odds ratio 72.1, $P < 2 \times 10^{-6}$). Table 3 presents the HLA typing of the 32 Japanese IAS patients so far examined [16]. Analysis of the nucleotide sequences showed that all of the patients with IAS had DRB1*0406, DQA1*0301 and DQB1*0302 compared with only 14% of the controls having this haplotype (odds ratio 385, $P < 1 \times 10^{-10}$). Uchigata et al. [17] reported that all 13 patients with Graves' disease who developed IAS by MTZ therapy possessed a specific allelic combination, Bw 62/Cw4/DR4 carrying DRB1*0406, whereas only one of 50 Graves' disease patients without

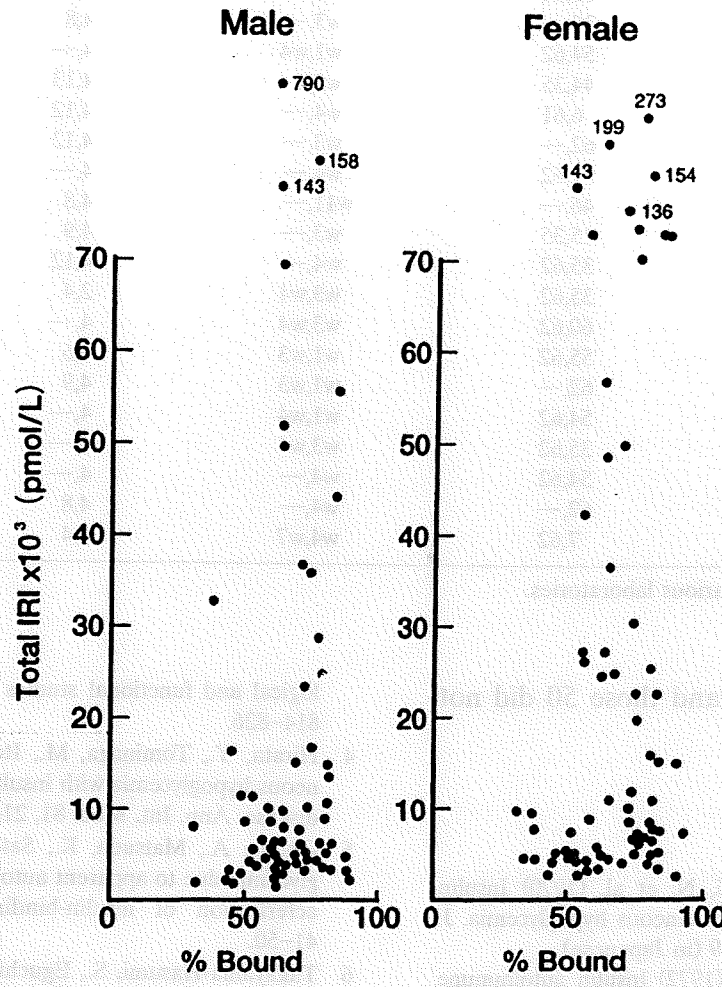

Fig. 1. Total extractable immunoreactive insulin, and ^{125}I-insulin binding % of the sera of male and female patients, immediately after diagnosis of insulin autoimmune syndrome. The methods for the IRI and ^{125}I-human insulin binding assay have been described elsewhere [11]. At diagnosis of IAS, the peak of the hypoglycemic attacks had been passed. The normal range of total IRI and ^{125}I-insulin binding was <71.8 pmol/l and $<5\%$, respectively.

Table 3
Serological HLA typing of Japanese patients with insulin autoimmune syndrome

Pt. no.	HLA				
	A	B	C	DR	DQ
1	2,26	40,62	w4,—	4,—	NT
2	11,33	44,62	w4,—	4,13	1,3
3	11,24	44,62	w4,—	4,9	NT
4	2,24	51,62	w3,—	4,12	3,—
5	11,24	62,—	w4,—	4,—	3,—
6	11,24	60,62	w4,—	4,9	NT
7	11,—	54,52	w1,w4	4,8	1,3
8	11,33	44,62	w4,—	4,9	3,—
9	11,31	16,62	w4,w7	2,4	NT
10	24,26	35,61	w3,—	4,9	NT
11	24,26	62,—	w3,w4	2,4	NT
12	24,26	62,—	w4,—	4,—	NT
13	24,33	17,62	w3,w4	4,6	1,3
14	2,11	61,62	w4,—	4,9	3,—
15	26,—	35,—	w3,—	4,8	3,—
16	24,—	54,62	w1,w4	4,—	3,—
17	2,33	44,35	w3,—	4,13	NT
18	11,24	6,61	w4,—	4,12	3,7
19	24,31	62,—	w3,—	4,12	3,7
20	2,11	51,62	w4,—	4,—	3,—
21	2,—	46,—	w11,—	4,8	1,3
22	2,24	15,35	w3,—	4,9	3,—
23	2,26	35,62	w4,—	4,12	NT
24	24,26	35,62	w3,w4	2,4	1,3
25	2,11	60,62	w3,w4	4,—	NT
26	2,11	55,62	w1,w3	4,6	1,3
27	11,—	62,—	w1,w3	4,9	NT
28	24,31	54,62	w1,w4	4,—	3,4
29	11,26	35,62	w3,w4	4,—	3,4
30	11,24	54,62	w4,—	4,—	3,4
31	2,11	62,—	w4,—	4,8	1,3
32	11,31	7,62	w4,w7	1,4	NT

HLA typing was performed in various laboratories.
NT, not tested.

IAS had Bw62/Cw4/DR4 and those 50 did not possess DRB1*0406.

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Diabetes Research and Clinical Practice, 10 (1990) 211–214
Elsevier

DIABET 00437

Insulin autoimmune syndrome is the third leading cause of spontaneous hypoglycemic attacks in Japan

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(Received 10 February 1990)
(Revision received 14 May 1990)
(Accepted 16 May 1990)

Summary

From 1979 to 1981, questionnaires were sent to 2094 hospitals throughout Japan to investigate the causes of severe hypoglycemic attacks other than the administration of oral hypoglycemic agents or insulin preparations. The survey revealed three main causes for the attacks, of which the first was insulinoma, the second extrapancreatic neoplasms, and the third was insulin autoimmune syndrome (IAS), in descending order. Seven years later, a second survey was carried out, which showed the order of the three disorders as the cause of the hypoglycemic attacks to be the same as in the first survey. In both studies it was suggested that the IAS was frequently induced by thiol compounds.

Key words: Hypoglycemic attack; Insulin autoimmune syndrome; Insulin auto-antibody; Insulinoma

Introduction

Since Hirata et al. [1] reported the first case of insulin autoimmune syndrome (IAS) in 1970, 140 cases of IAS have been found in Japan. This syndrome is characterized by transient hypoglycemia and the discovery of the anti-insulin auto-antibodies in the sera of patients who had not received insulin. Although the pathogenesis of this syndrome remains unclear, massive amounts of insulin can be extracted from the patients' sera during their hypoglycemic attacks because of the high titer of anti-insulin autoantibodies. In this study, in order to find out the incidence of IAS as a cause of spontaneous hypoglycemia in Japan, we sent questionnaires to 2094 hospitals asking about their experience with hypoglycemic attacks.

Method

Questionnaires were sent to the directors of the departments of internal medicine at 2094 hospitals in Japan, which included 309 public or private medical college hospitals, 1415 public hospitals with more than a hundred beds, and 325 private hospitals with more than two hundred beds. In the first survey we asked for all the cases that led

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to a spontaneous hypoglycemic attack, excluding reactive hypoglycemia, and in the second survey we only requested the number of patients with insulinoma, extrapancreatic neoplasms and IAS, as these were found to be the major causes of hypoglycemic attacks in the first survey. The first survey was held in 1982 and covered 3 years, from 1979 to 1981; and the second was held in 1988, and covered the 3 years from 1985 to 1987.

Results and Discussion

The result of the first survey showed that the total number of attacks was 350, the leading causes are shown in Table 1. The most frequent causes were insulinoma (125 cases), extrapancreatic neoplasms (92 cases), and IAS (41 cases), which are followed by alcohol, hypopituitarism, severe liver damage, adrenal insufficiency etc. In the second survey the questionnaires were answered by 1033 of the 2094 departments of internal medicine (50.4%). 769 of the 1033 departments (74.4%) had no experience with spontaneous hypoglycemic attacks, and 264 departments had had more than one experience with an attack. The second survey was repeated especially to determine the order of the three main causes, as is shown in Table 2. The results revealed them to be in the same descending order as in the first survey. From the results of the both studies we concluded that the main causes of spontaneous hypoglycemic attacks had not changed within the last decade in Japan. This fact is significant, since it suggests that IAS is a common cause of spontaneous hypoglycemia in Japan. In both studies the number of IAS cases was about one third of the insulinoma cases, and therefore, Japanese doctors should be careful not to misdiagnose IAS with insulinoma.

The characteristics of the IAS cases collected from the two surveys are shown in Table 3. This syndrome is detected in both sexes, and the age distribution was similar in males and females. Interestingly, in the first survey, only 9 out of 41 cases (21.9%) of IAS occurred after the patients used thiol compounds, whereas half of the patients used thiol compounds before their first hypoglycemic attack in the second survey. The reason for this discrepancy remains unclear. The first case of IAS that occurred after the use of methimazol was reported by Hirata et al. [2], in 1974, and the first case after the use of tiopronin was reported by Ichihara et al. [3] in 1977. Moreover, Takei et al. [4] reported that the production

TABLE 1

Causes of spontaneous hypoglycemic attacks in Japan (results from the first survey)

	No. of cases (%)
Insulinoma	125 (35.7)
Extrapancreatic neoplasms	92 (26.3)
Insulin autoimmune syndrome	41 (11.7)
Alcohol-induced	23 (6.6)
Hypopituitarism	16 (4.6)
Severe liver damage	10 (2.9)
Adrenal insufficiency	7 (2.0)
Septicemia	4 (1.1)
Chronic renal failure	4 (1.1)
Chronic leukemia	3 (0.9)
Anorexia nervosa	3 (0.9)
Glycogenoses	2 (0.5)
Insular hyperplasia	1 (0.3)
Disopyramide-induced	1 (0.3)
Brom acid intoxication	1 (0.3)
Unknown	27 (7.7)
Total	350 (100)

TABLE 2

Number of cases with the three main causes inducing spontaneous hypoglycemic attacks in two separate periods

	1st survey (1979–1981) No. of cases (%)	2nd survey (1985–1987) No. of cases (%)
Insulinoma	125 (48.4)	93 (50.3)
Extrapancreatic neoplasms	92 (35.6)	56 (30.2)
Insulin autoimmune syndrome	41 (15.9)	36 (19.5)
Total number of three causes	258 (100)	185 (100)

TABLE 3
Characteristics of the IAS cases collected from two separate surveys

	No. of cases	Sex	Age	No. of cases after the use of thiol compounds			
				Methimazol	Tiopronin	Glutathione	Total (%)
1st survey	41	18 M 23 F	53.3 ± 16.5 52.5 ± 14.9	7	2	0	9 (21.9%)
2nd survey	36	19 M 17 F	57.1 ± 14.6 59.9 ± 18.4	6	9	3	18 (50.0%)

of anti-insulin auto-antibodies was stimulated in patients that were using methimazol, even if these patients did not have a hypoglycemic attack. These observations suggest that thiol compounds might change the structure of insulin, and that this altered form may have greater antigenicity than intact insulin. Although Seino [5] reported by reverse-phase HPLC the existence of an abnormally migrated insulin in the sera of two out of three IAS patients, we could not detect even a minimal change in insulin structure by reverse-phase HPLC in the sera of six IAS cases [6]. On the other hand, the evidence that the supplementation of thiol compound to the isolated perfused rat pancreas increases the insulin secretary action of glucose [7] may possibly help to explain the pathogenesis of the hypoglycemic attacks in IAS; however, the mechanism generating insulin auto-antibody and the hypoglycemic attacks in IAS cases remains unknown.

Another interesting problem is that only a few cases of IAS have been reported in Europe [8–10], and the U.S.A. [11–13], although more than 100 cases of IAS have been reported in Japan since 1970. This discrepancy may be explained by the genetical differences between Caucasians and Japanese. We have analysed the results of HLA typing in 26 Japanese IAS cases to try to answer this problem and to define the pathogenesis of this syndrome [14]. The frequencies of HLA B15 (Bw62), Cw4 and DR4 were significantly increased when compared to the control. This result suggested that some specific types of HLA antigens might be associated with the susceptibility of this syndrome in Japan.

Acknowledgement

The English correction of this manuscript by Miss Barbara Levene is appreciated. This work was supported by a grant from the Hagedorn Award from the Japanese Diabetes Association for Y.H.

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Case Report

Severe hypoglycaemia in a person with insulin autoimmune syndrome accompanied by insulin receptor anomaly type B

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Accepted 25 March 2007

Abstract

Aims A rare case of the insulin autoimmune syndrome (IAS) accompanied by insulin receptor anomaly is reported.

Methods Antibodies to insulin and insulin receptor were determined in the patient with severe hypoglycaemia before and after the treatment with prednisolone.

Results Titers of antibody to insulin and insulin receptors were 73.0% and 41.5%, respectively. Drug-induced lymphocyte stimulation tests were all negative for the suspicious drugs. Her HLA-DR was DRB1*0403/04051. Following steroid therapy, the formation of antibodies was suppressed and alleviated her symptoms. Scatchard analysis yielded findings specific to polyclonal antibodies.

Conclusions The changes in autoantibodies resulted in alleviation of the hypoglycemic symptoms as a result of steroid therapy.

Diabet. Med. 24, 1279–1281 (2007)

Keywords autoimmune, hypoglycaemia, insulin, receptor, syndrome

Abbreviations ACTH, adrenocorticotrophic hormone; B/F, bound/free; GH, growth hormone; IAS, insulin autoimmune syndrome; IRI, immunoreactive insulin; TSH, thyroid stimulating hormone

Introduction

The insulin autoimmune syndrome (IAS), reported in 1970 by Hirata *et al.* [1], is characterized by spontaneous hypoglycaemic episodes, despite the absence of previous insulin injection, detection of high levels of insulin in blood and high titres of anti-insulin antibody. The pathogenesis remains unknown. Insulin receptor anomalies [2], however, often complicate autoimmune disease and cause hyperglycaemia accompanied by markedly severe insulin resistance. Here, we report a rare case of IAS accompanied by insulin receptor anomaly where severe hypoglycaemia developed.

Case report

A 74-year-old woman had massive cold sweats and felt dizzy while walking. She had a past history of osteoarthritis in both knee joints, and had previously experienced vertigo. Her blood glucose level was low at 2.2 mmol/l, and her insulin level was extremely high. Anti-insulin antibody titre determined by the ^{125}I-insulin binding [3] to patient's serum was also abnormally high. The woman had not previously received insulin. Her BMI was 26.7 kg/m^2. Her conscious level was normal, and physical examination was essentially negative. Plasma concentrations of growth hormone (GH), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), free T3 and T4, and cortisol levels were all within the normal range. Anti-thyroglobulin antibody titre was

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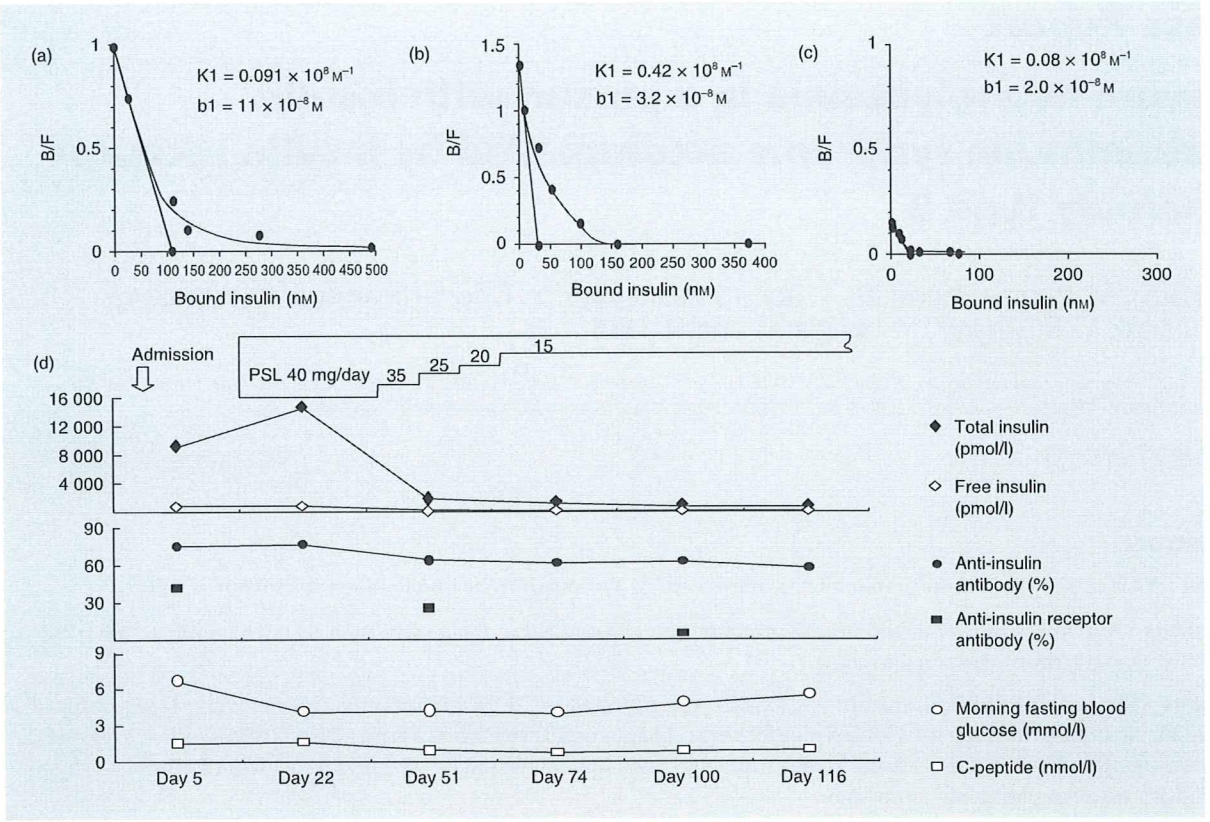

FIGURE 1 Scatchard analysis for insulin and auto-antibodies. Scatchard analysis for insulin auto-antibody in the patient was performed using ^{125}I-human insulin and the patient's serum treated with dextran-coated charcoal, as described in the literature [4]. (a) Before treatment with prednisolone (PSL); (b) 38 days after treatment with prednisolone; (c) 87 days after treatment with prednisolone; (d) clinical course and effects of prednisolone on the patient's antibodies. B/F, bound/free.

abnormally high, but other autoantibodies were negative. Anti-insulin receptor antibody was determined by the method described elsewhere [2] using cultured IM-9 cells. The patient's serum inhibited the binding of ^{125}I-insulin to IM-9 cells by 41.5%. Her human leukocyte antigen-DR (HLA-DR) was DRB1*0403/04051. An oral 75-g glucose tolerance test showed a diabetic pattern. As insulin antibodies were positive, free immunoreactive insulin (IRI) was measured and also showed high concentration at 720 pmol/l. After an overnight fast, C-peptide was 1.51 nmol/l. Thus, we diagnosed IAS accompanied by insulin receptor anomaly.

Drug-induced lymphocyte stimulation tests (DLST) were performed by measuring the uptake of ^{3}H-thymidine into patient's lymphocytes incubated with the tested drug. The test was negative for all of the drugs previously administered (loxoprofen sodium, etizolam, betahistine mesilate, eperisone hydrochloride, kallidinogenase and troxipide). Drugs possessing the sulfhydryl (SH) group have been assumed to be responsible for IAS, but hypoglycaemia continued after all drugs were withdrawn. Frequent measurements for glucose and food intake every 2 h at night to avoid hypoglycaemia made her irritable. Thus, prednisolone was started, initially at 40 mg daily and gradually decreased thereafter. Following steroid therapy, the formation of antibodies to insulin and insulin receptors was suppressed, leading to marked changes in total insulin, free insulin and C-peptide levels. Scatchard analysis [4] using whole serum yielded findings specific to polyclonal antibodies. The affinity constant (K1) and binding potential (b1) at the high-affinity site was 0.091 k × 10^{-8} M^{-1} (K1) and 11 × 10^{-8} M (b1) before treatment with prednisolone, 0.42 k × 10^{-8} M^{-1} and 3.2 × 10^{-8} M 38 days after treatment, and 0.08 k × 10^{-8} M^{-1} and 2.0 × 10^{-8} M after 87 days (Fig. 1). Paralleling this decrease in antibodies, the frequency of hypoglycaemic episodes decreased, and finally ceased.

Discussion

Uchigata *et al.* demonstrated a strong correlation between ISA and HLA-DR4, which was found in 96% of Japanese patients, and DRB1*0406 was closely related [5]. The present case was DRB1*0403, a relatively rare genotype. Insulin receptor anomaly type B is often complicated by other autoimmune disorders, and the high titre of anti-thyroglobulin antibody suggests autoimmune disease was present. Antibody to insulin

receptors is multiclonal in nature and exerts diverse physiological actions. The normal blood glucose level, despite the abnormally high free insulin level on admission, suggests that the present case was resistant to insulin as a result of the antibodies to insulin and insulin receptors. Regarding the mechanism for onset of hypoglycaemia in the present case, two possibilities exist: (i) hypoglycaemia induced by IAS, and (ii) hypoglycaemia as a result of the insulin-like action of the antibody to insulin receptors. It remains unclear how the two antibodies were involved in the hypoglycaemic episodes. However, the diabetic pattern of the oral glucose tolerance test (OGTT) in spite of high free IRI and C-peptide suggest that the latter possibility is unlikely.

In conclusion, the changes in autoantibodies in our patient with severe hypoglycaemia because of IAS and insulin receptor anomaly type B resulted in alleviation of the symptoms of hypoglycaemia and improvement in total and free insulin and C-peptide levels, apparently as a result of steroid suppression of the formation of anti-insulin antibody and antibody to insulin receptors.

Competing interests

None to declare.

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