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Case Report

Insulin Resistance Type A Syndrome in a 12-year-old Girl

Norihiko YOKOMORI, Masato TAWATA, Kaoru AIDA, Zentoshi ABE[1)], Yoshiaki HORI[1)], and Toshimasa ONAYA

The Third Department of Internal Medicine, and [1)]Department of Dermatology, University of Yamanashi Medical School, Tamaho, Yamanashi 409-38, Japan

Abstract: An obese 12-year-old girl with acanthosis nigricans was referred to the hospital because of hyperinsulinemia. She was 156 cm tall and her body weight was 67.5 kg. Physical examination revealed that she had acanthosis nigricans in the neck, axillary and inguinal regions. She also had hirsutism over the extremities. Endocrinological data showed mild elevations of plasma luteinizing hormone, testosterone and androstenedione and urinary testosterone. A significant reduction of ^{125}I-insulin binding to her red blood cells was observed. Serum anti-insulin antibodies or anti-insulin receptor antibodies were not detected. The clinical and laboratory data suggested that this patient had a syndrome known as Type A insulin resistance.

Key words: Insulin Resistance Type A, Acanthosis Nigricans, Obesity, Hirsutism

INTRODUCTION

Insulin resistance, an uncommon complication of diabetes mellitus[1)], can almost always be ascribed to development of anti-insulin antibodies, or other endocrinal disorders such as acromegaly[2)] and Cushing's syndrome[3)].

Insulin resistance has also been reported in some patients with increased insulinase activity at injection sites[4,5)] and in obese patients[6-8)]. In addition, several types of peripheral tissue resistance to insulin action have recently been reported as unusual forms of diabetes or impaired glucose tolerance. These types can be divided into three unique clinical syndromes: Type A, insulin receptor is defective; Type B, circulating antibodies to insulin receptors[9)] and Type C, defects in insulin action distal to the binding to its receptor[10)]. Another type of insulin resistance has also been reported in patients with biologcally less active insulin molecule, who however retain almost normal immunoreactivity[11-13)]. In this type of disorder, however, it is reported that patients respond normally to exogenous insulin.

In this paper, we report on a 12-year-old obese and hyperpigmented girl with hyperinsulinemia, who appeared to have Type A insulin resistance syndrome.

MATERIALS AND METHODS

^{125}I-Insulin was obtained from Amersham Japan. Human insulin was donated by Shionogi Pharmaceutical Co., Ltd. Red blood cells were obtained in the presence of heparin and washed with cold saline by centrifugation and resuspension, repeated three times. After adjusting the erythrocyte number to 3×10^6/mm^3, the insulin binding study was done according to the method used by Flier et al[14)].

CASE HISTORY AND PHYSICAL EXAMINATIONS

This 12-year-old girl was the product of a full-term, uncomplicated pregnancy and deliv-

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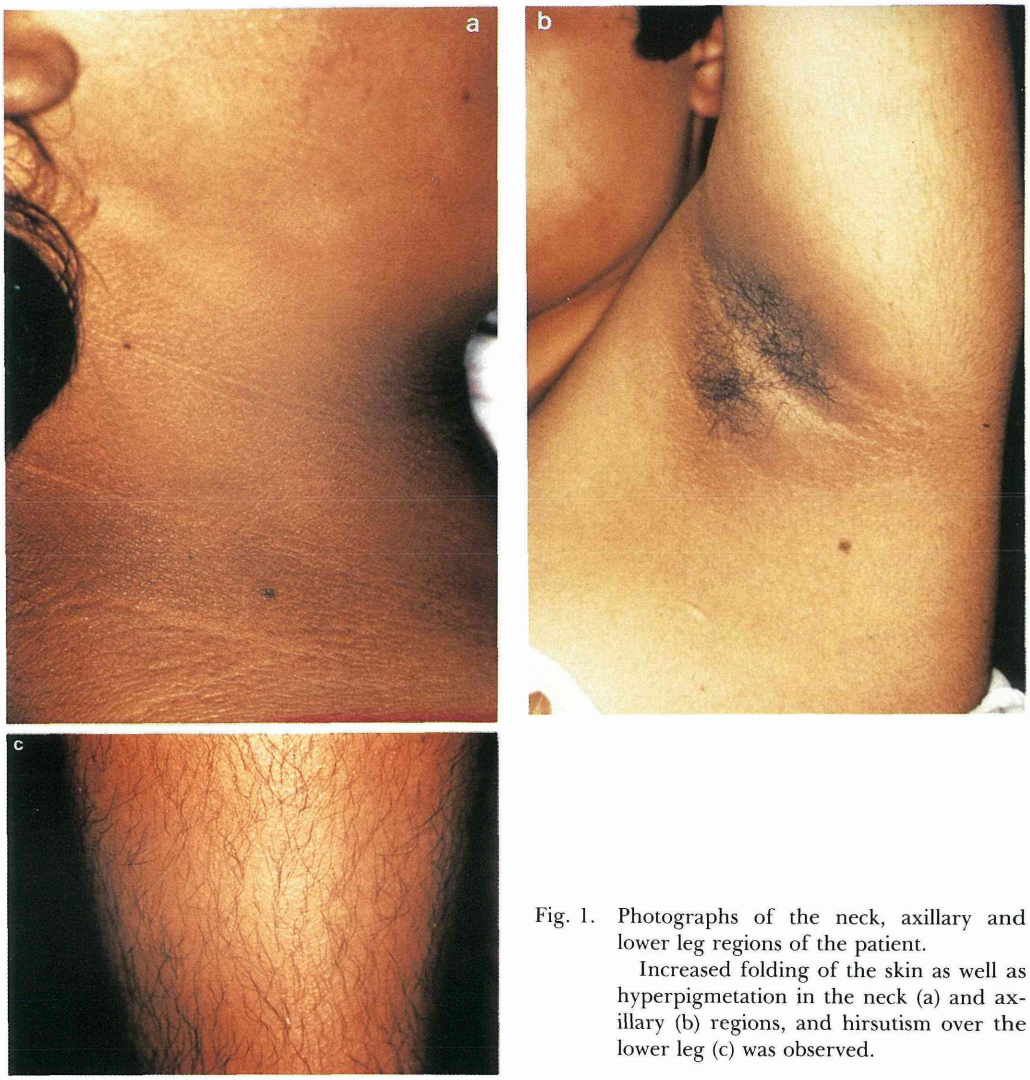

Fig. 1. Photographs of the neck, axillary and lower leg regions of the patient.
Increased folding of the skin as well as hyperpigmetation in the neck (a) and axillary (b) regions, and hirsutism over the lower leg (c) was observed.

ery. At the age of 10, she was noted to have a marked increase in her body hair and skin foldings, with hyperpigmentation over the neck, axillary and inguinal regions. In March 1985, the patient was referred to the Department of Dermatology, University of Yamanashi medical School. She was diagnosed as having acanthosis nigricans, by skin biopsy. Her family history and past history were unremarkable. Although menarche began at the age of 10, her menstruation thereafter has been irregular.

On admission, physical examination revealed a healthy-looking girl, 156 cm tall and weighing 67.5 kg. She had welldeveloped breasts and pubic and axillary hairs. The circumference of the lips, the neck (Fig. 1, a), axillary (Fig. 1, b) and inguinal regions showed increased skin folding with hyperpigmentation, diagnosed as acanthosis nigricans. She was also noted to have increased body hairs, particularly in the lower leg (Fig. 1, c) and forearm regions. External genitalia and uterus were normal and there was no evidence of polycystic ovaries under ultrasound examination. Neither a chest X-ray nor an electrocar-

Table 1. Laboratory data

WBC	5100/mm^3	TP	7.3 g/dl
RBC	532×10/mm^3	Alb	5.2 g/dl
Hgb	15.3g/dl	γ-globulin	0.9 g/dl
Ht	42	Ch-E	1.27 ΔpH
Platelets	26×10^4/mm^3	ZTT	3.9 KU
		T. Bil	1.0 mg/dl
		Al-P	232 IU/l
Erythrocyte sedimentation Rate	15mm/hr	LAP	46 IU/l
		LDH	273 IU/l
LE test	(−)	γ-GTP	15 IU/l
Anti-nuclear antibodies	(−)	GOT	12 IU/l
		GPT	13 IU/l
RA	(−)	TG	111 mg/dl
		T. Chol	155 mg/dl
		BUN	13 mg/dl
		Crtn	0.5 mg/dl

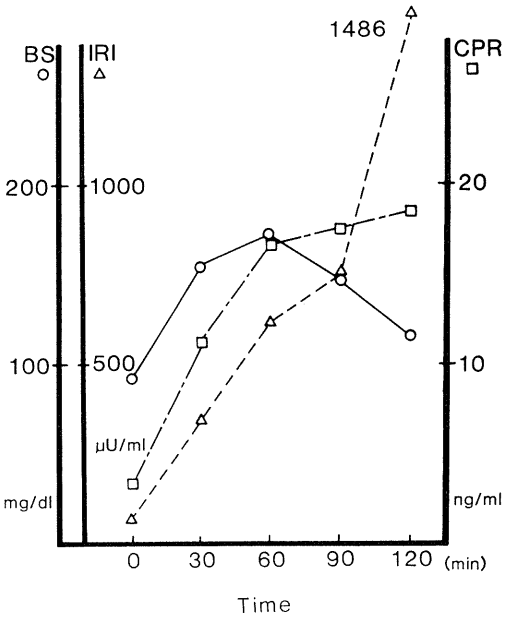

Fig. 2. 75 g oral glucose tolerance test.
After overnight fasting, 75 g glucose was ingested and BG (blood glucose), IRI (immunoreactive insulin) and CPR (C reactive peptide) were determined.

diography disclosed any abnormalities.

Laboratorical Data

As indicated in Table 1, the results of routine laboratory examinations were within normal limits. Her serum γ-globulin and erythrocyte sedimentation rates were within the normal range, and serological tests were all negative.

Table 2. 75g oral glucose test of family members

	Father		Mother		Sister	
	BG	IRI	BG	IRI	BG	IRI
0'	100	8.1	95	8.5	92	7.9
30'	164	70	99	29		
60'	152	58	111	115		
90'	82	27	92	24		
120'	104	67	114	21	86	19

BG (blood glucose): mg/dl
IRI (immunoreactive insulin): μU/ml

Fig. 2 shows the results of a 75 g oral glucose tolerance test. The plasma glucose test showed mildly impaired glucose tolerance with 171 mg/dl at 60 min. In spite of this mild abnormality in plasma glucose, plasma immunoreactive insulin (IRI) progressively increased from its basal value of 68 μU/ml to 1486 μU/ml at 120 min. Plasma C peptide immunoreactivity (CPR) also showed an exaggerated response. The results of oral glucose tolerance tests on her parents and sister revealed no abnormality except for the mother who had a slightly increased IRI at 60 min (Table 2).

Table 3. Endocrinological data

Anti-insulin antibodies		5	(<12)*	%			
GH		<1		ng/ml			
Triiodothyronine		120		ng/dl			
Thyroxine		7.8		ug/dl			
		0'	15'	30'	60'	120'	
TRH test	TSH	1.6	13	13	7.2	2.7	uU/ml
	PRL	14	73	42	26	17	ng/ml
Plasma	Cortisol	8 : 00		14 : 00	23 : 00		hr
	ACTH	22.7		17.8	2.3		ug/dl
	17-	<20		pg/ml			
Urinary	OHCS	8.1–14		mg/day			
	17-KS	6.7–8.1		mg/day			
		0'	15'	30'	60'	120'	
LHRH test	LE	38	195	212	152	143	mIU/ml*
	FS H	13	26	28	28	26	mIU/ml*
Palsma	Testosterone	150	(10–85)**				ng/dl
	Androstenedion	2.35	(0.15–2.05)**				ng/dl
Urinary	Testosterone	17.7	(2–10)**				ug/day

* LH and FSH are mesured by radioimmunoasssay.
**The values in parentheses indicate normal ranges

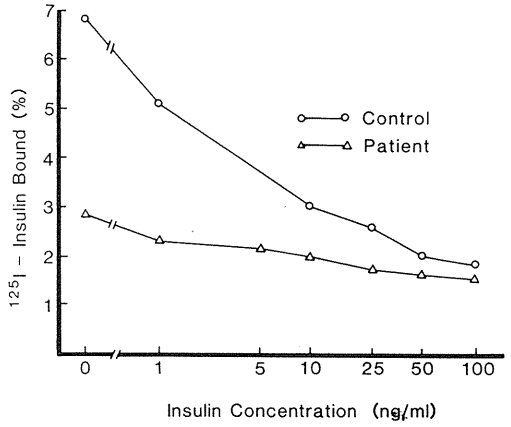

Fig. 3. ^{125}I-Insulin binding to erythrocytes. The ordinate indicates the percentage of bound ^{125}I-insulin and the abscissa indicates the concentrations of insulin logarithmically.

Because of the patient's unexpected hyperinsulinemia, she was placed for further evaluation. Her circulating anti-insulin antibodies were within normal ranges (Table 3).

In order to clarify the mechanism of hyperinsulinemia, the interaction of insulin with its receptor was evaluated by measuring the binding of ^{125}I-insulin to her erythrocytes. As shown in Fig. 3, there was a marked decrease in ^{125}I-insulin binding to erythrocytes in this patient compared to a control subject.

The binding of ^{125}I-insulin to erythrocytes did not show any significant change in the presence or absence of patient's plasma (data not shown).

Table 3 shows other endocrinological data from the patient. Thyroid function and glucocorticoid circadian rhythm were within normal limits. However, mild elevations of plasma luteinizing hormone (LH) (212 mIU/ml at 30 min), testosterone (150 ng/dl) androstenedione (2.35 ng/dl), and urinary testosterone (17.7 μg/day) were observed.

DISCUSSION

the clinical features of this patient were early onset of hirsutism, acanthosis nigricans and obesity. There was no evidence of autoimmune disorders. The laboratory examination revealed marked hyperinsulinemia in the absence of anti-insulin antibodies.

The binding study of ^{125}I-insulin to erythrocytes showed a marked decrease of insulin binding to the receptors. It is possible that the decreased binding of ^{125}I-insulin to the receptors may have resulted from the circulating anti-receptor antibodies. Therefore we examined the binding of ^{125}I-insulin to erythrocytes in the presence of the patient's plasma, according to the method of Flier et al[15]. The result of this study ruled out the presence of anti-insulin receptor antibodies. Based on these data, we diagnosed this patient as having Type A insulin resistance syndrome.

Patients with Type A insulin resistance syndrome are usually characterized by several signs such as obesity, hirsutism, acanthosis nigricans and polycystic ovaries. Although we could not detect polycystic ovaries in this patient, mild elevations of plasma LH, testosterone and androstenedione, and urinary testosterone suggest the possibility of this disease.

Type A insulin resistance syndrome is considered to be a genetically inherited disease[16]. Recently, the cloning of the complementary DNA of the normal human insulin receptor was reported by two groups[17,18]. These reports made it possible to investigate the mutations of the inslulin-receptor gene in a patient with leprechuanism[19], and in a patient with Rabson-Mendenhall syndrome[20].

As far as Type A insulin resistance syndrome is concerned, genetical analysis has been reported only in one case[21] so far, in which the authors found that there were two single-base mutations in the insulin-receptor gene.

In spite of no apparent hyperinsulinemia, the mother of this patient also showed decreased ^{125}I-insulin binding to erythrocytes (data not shown). Thus, we think that the insulin resistance of this patient may have been inherited from her mother. Further genetical analysis of this patient and her mother are now underway.

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