Familial Insulin Resistance and Acanthosis Nigricans

Presence of a Postbinding Defect

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SUMMARY

Type A insulin resistance, associated with acanthosis nigricans and menstrual irregularity, has been ascribed to a decreased concentration of insulin receptors. We now report four affected females from one family, a mother and three daughters (including identical twins) who appear to have the type A syndrome. Two of the kindred had no apparent ovarian dysfunction, while the other two had hyperprolactinemia without other findings of polycystic ovary disease, suggesting a genetic disease with variable penetrance. All had normal erythrocyte and monocyte insulin binding. Insulin dose-response studies to assess glucose metabolism and insulin sensitivity were performed in the affected twins. The dose response to insulin was shifted to the right with a decrease in maximal response. These results are consistent with a postbinding defect in insulin action in these patients. DIABETES 1986; 35:33–37.

The association of acanthosis nigricans and insulin resistance is well documented,[1,2,8] and has been described as a component of a number of distinct familial syndromes.[3–7] When these findings occur in young females with ovarian dysfunction, the syndrome has been called type A insulin resistance.[1,2,8] The etiology of the insulin resistance has not been clearly established, but reduced concentrations of insulin receptors on monocytes and erythrocytes have been reported.[2] On the other hand, a patient, who otherwise fulfilled the criteria of type A insulin resistance, has been reported to have normal binding and was presumed to have a postbinding defect,[9] although no insulin dose-response studies were carried out to confirm this speculation.

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We now report four females, a mother and three daughters (including identical twins), who appear to have type A insulin resistance. In an effort to gain further insight into the mechanism of their insulin resistance, insulin binding to monocytes and/or erythrocytes was determined in three of the subjects and insulin dose-response curves were carried out in the twins. The lack of an abnormality in either monocyte or erythrocyte insulin binding, and the decrease in maximal insulin-stimulated glucose metabolism, provides strong evidence of a postbinding defect in insulin action in this family.

CASE REPORTS

Patient IIA. The proband was a 14 6/12-yr-old white female at the time of initial evaluation (Figure 1). At age 12 yr she underwent menarche, but regular menstrual periods were never established. Shortly afterward, she began having muscle cramps in her lower extremities, bitemporal throbbing headaches, acne, and pigmentation under her arms and neck.

At the time of our initial evaluation, the proband was a short, muscular-appearing young woman with coarse facial features. Her pulse was 80 beats/min, blood pressure 150/70 mm Hg, height 153 cm, and weight 62.4 kg. She was 112% ideal body weight (1983 Metropolitan Life Insurance Tables). Her breasts and pubic hair were Tanner stage IV. She had severe acanthosis nigricans in both axillae, around her neck, and over her lower abdomen. Acne and mild hirsutism were also present on her back and shoulders. There was no frontal balding or clitoral hypertrophy. Her familial lineage is Eastern European, with frequent intermarriage within a distinct cultural group occurring over hundreds of years. By history, there are several other family relatives on the maternal side in addition to those reported below with asymptomatic, increased pigmentation suggestive of acanthosis nigricans, similar coarse facial features, and muscle hypertrophy.

Patient IIB. This subject is the identical (by HLA haplotyping) twin of Patient IIA, and was 15 yr of age when first seen. She had menarche at age 12 yr and has had regular monthly menstrual periods through the time of the present report (age

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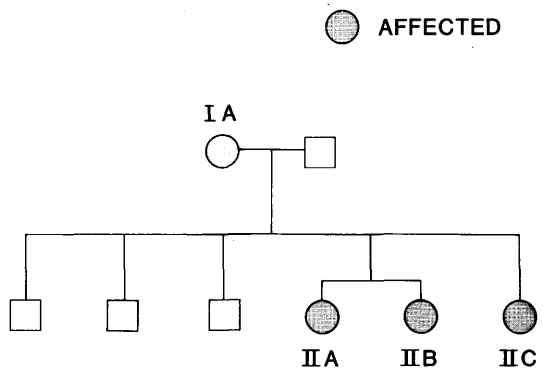

FIGURE 1. Nuclear family with acanthosis nigricans and insulin resistance.

19 yr). Like her sister, she had headaches, muscle cramps, coarse facial characteristics, and was a muscular young woman. Her height was 147.5 cm and her weight 55.5 kg, and she was 100% ideal body weight. Her blood pressure was 148/74 mm Hg and pulse 80 beats/min. She had acanthosis nigricans in both axillae, neck, and lower abdomen. There was no frontal balding or clitoral hypertrophy, but she also had acne and mild hirsutism on her back and shoulders.

Patients IIC and IA. The older sister (1.5 yr older than the proband) and mother (age 38 yr at the time of the initial evaluation of patient IIB) of the proband were asymptomatic with a history of normal menstrual periods and recalled the appearance of acanthosis nigricans at about the time of menarche. Both had coarse facial features, and were very broad shouldered and muscular. Acanthosis nigricans was present in the axillae, under the neck, and in the superpubic area in both women. Neither had clitoral hypertrophy or frontal balding.

All four women had small breasts without galactorrhea. A summary of the symptoms and signs of these four patients is listed in Table 1.

Laboratory investigations in the twins. Selected laboratory data for the twins are provided in Table 2. Plasma prolactin concentrations were elevated in both twins, but were normal in subjects IIC and IA. Plasma-free testosterone concentrations were normal. LH, FSH, and the LH/FSH ratio were normal. Twenty-four-hour urinary 17-ketosteroids were slightly elevated with increased excretion of androsterone, etiocholanolone, pregnanetriol, 11-ketoetiocholanolone, and 11-hydroxyandrosterone in both twins. This abnormal steroid excretion was suppressed with dexamethasone (0.75 mg q.d.).

TABLE 1
Familial syndrome of acanthosis nigricans and insulin resistance

Patient	IA	IIA*	IIB	IIC
Symptoms				
Headaches	−	+	+	+
Muscle cramps	−	+	+	−
Abnormal periods	−	+	−	−
Signs				
Acanthosis nigricans	+	+	+	+
Muscle hypertrophy	+	+	+	+
Hirsutism	−	+	+	−
Masculinization	−	+	+	−

+, Present; −, not present; and *, proband.

TABLE 2
Hormone data in the twins

		IIA	IIB	Normals*
Corticosteroids	a.m.	17	11	7–28
(μg/dl)	p.m.	9	Not done	2–18
Growth hormone (ng/ml)		<1.0	4.0	0–10
Somatomedin-C (U/ml)		1.2	1.2	0.71–4.1
Epinephrine (pg/ml)		91	51	<110
Norepinephrine (pg/ml)		304	273	70–750
Prolactin (pg/ml)		35	40	0–23
Free testosterone (ng/dl)		1.6	1.7	0.3–1.9
24-H urinary free cortisol		82	65	24–108
24-H urinary 17-ketosteroids		18	18	4–17

*Mayo Clinic Laboratory normals are listed.

Pelvic examinations and ultrasound, head CAT scans with special pituitary views, plasma magnesium concentrations, and electromyography were all normal. HLA typing predicted a 99.7% chance of homozygosity.

METHODS

Oral glucose tolerance was assessed by giving 1 g of glucose/kg, while i.v. glucose tolerance was assessed with 0.33 g of glucose/kg infused over 2 min. Erythrocyte insulin binding was measured by the method of Gambhir et al.,[10] and monocyte insulin binding by the method of DeMeyts.[11] Anti-insulin receptor antibodies were screened for by the method of Flier et al.[12] The euglycemic insulin clamps were performed as previously described by Rizza et al.,[13] and were carried out on twins IIA and IIB when they were age 15 yr. To estimate lean body mass, total body water was assessed using the method of Schloerb modified for ^3H_2O.[14] Normal data are expressed as mean ± 1SD unless otherwise stated.

RESULTS

While all four subjects had normal oral glucose tolerance (Figure 2A) when compared with 15 normal adult women[15] whose results have been reported from our laboratory, their plasma insulin concentrations were elevated [peak postglucose immunoreactive insulin (IRI) concentrations of 244–1010 μU/ml compared with 90 ± 4 μU/ml for controls], suggesting the presence of insulin resistance. Normal i.v. glucose tolerance (Figure 2B) with elevated plasma insulin concentrations when compared with five normal adults reported from our laboratory[16] (peak post-i.v. glucose IRI of 253–680 μU/ml compared with 101 ± 25 μU/ml for controls) was also found in the three patients studied.

Insulin binding studies carried out on the mother and twins yielded binding in the lower part of normal range—erythrocytes: IA, 3.8%; IIA, 3.0 %; IIB, not done; and normal adults, 3.5–7.5%; monocytes: IA, 8.3%; IIA, 7.0%; IIB, 9.0%; and normal adults, 7.0–9.0%. Incubation of plasma from the twins with normal erythrocytes did not alter insulin binding (data not shown).

During the euglycemic insulin clamps (see Figure 3), plasma glucose concentrations were maintained at 94 ± 1

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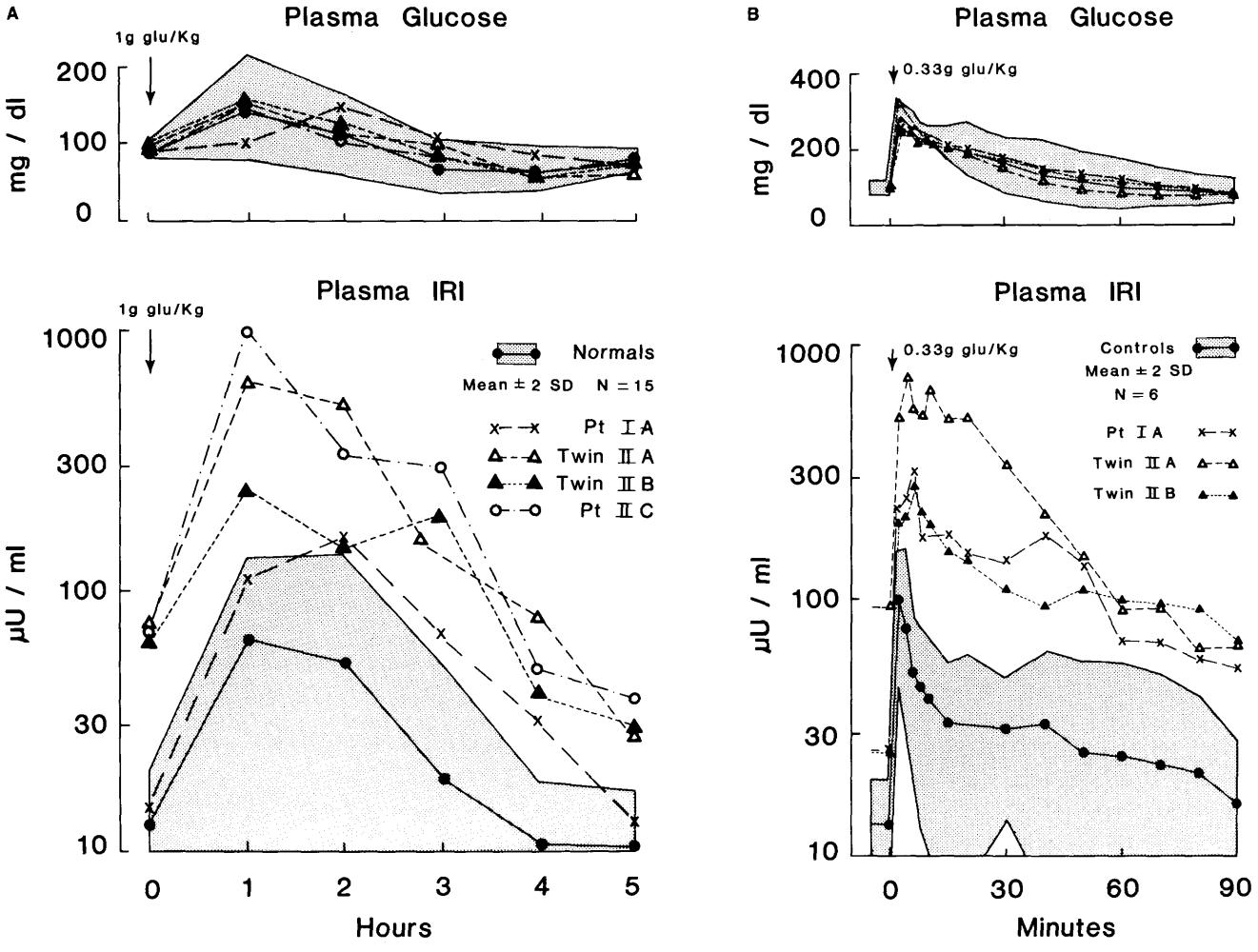

FIGURE 2. Plasma glucose and immunoreactive insulin concentrations after oral administration of 1 g of glucose/kg body wt (A), or 0.33 g of glucose/kg body wt i.v. (B). The mean ± 2SD of results obtained from 15 adult women for the oral administration and from five adults for the i.v. administration are included as controls.

(±1 SEM) and 95 ± 1 for twins IIA and IIB, respectively, compared with 95 ± 1 for the control patients.[13] The plasma IRI varied from 65 to 1600 μU/ml, depending on the rate of insulin infusion (see Figure 3). The insulin dose-response curves were shifted to the right (see Figure 4) with the half-maximal IRI responses of 131 and 210 μU/ml for twins IIA and IIB, respectively, versus 72 ± 20 μU/ml for the controls.[13] In addition, glucose infusion rates required to maintain euglycemia at 1600 μU/ml were decreased when compared with normals (5.7 and 8.3 mg/kg · min for twins IIA and IIB, respectively, and 12.0 ± 0.7 mg/kg · min for the controls).

Total body water estimates using ^3H_2O were elevated at 68% and 57% of total body weight for twins IIA and IIB, respectively, compared with the published mean (49%) for adult women.[17]

DISCUSSION

The increased plasma insulin concentrations observed during the oral and i.v. glucose tolerance studies despite normal plasma glucose concentrations suggest the presence of insulin resistance in each of these subjects. Insulin resistance was confirmed in the twins by the insulin dose-response studies. Assuming that human muscle (the predominant glucose-using tissue at supraphysiologic insulin concentration) possesses spare insulin receptors as has been demonstrated in animal muscle,[18] the decrease in maximal response strongly suggests the presence of a postbinding defect in insulin action.[19] This conclusion is supported by the near-normal erythrocyte and monocyte insulin binding observed in these patients. In addition, incubation of plasma from the twins with normal erythrocytes did not alter insulin binding, suggesting that anti-receptor antibodies are not the cause of the observed insulin resistance.

The total body water in the twins was increased compared with both published adult female and male norms,[14] consistent with increased muscle mass; therefore, it is unlikely that their insulin resistance could be ascribed to obesity.[20] Because of this increased muscle mass, we may actually have overestimated their maximal response in the insulin dose-response curves, since the glucose infusion rate is expressed per kilogram of total body weight. In addition, their insulin resistance did not seem to be due to elevations in cortisol, growth hormone, or epinephrine, since the concentrations of these hormones in their plasma were normal after an over-

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night fast and their urinary free cortisols were within the normal range (see Table 2).

The present studies, in conjunction with previous reports, emphasize the heterogeneity of type A insulin resistance. Most patients with this syndrome have decreased insulin binding,[1] whereas our patients had normal insulin binding but an insulin dose-response curve consistent with a postbinding defect in insulin action. Such a defect would be consistent with reports of two similar patients with type A insulin resistance and decreased insulin receptor kinase activity.[21,22] The heterogeneity of this disorder is further emphasized by the fact that, in contrast to other patients with genetic type A insulin resistance,[7] the transmittance appears to be dominant in the family that we are reporting.

Several aspects of the clinical presentation of this kindred merit comment. The mother, who is the oldest case of type A insulin resistance that we are aware of, has remained fertile and has not developed glucose intolerance. As has been reported in two siblings with type A insulin resistance, the twins also had muscle cramps.[7] The etiology of this problem and its relationship to the insulin resistance remain unknown. The cause of these cramps does not appear to be hypermagnesemia, as postulated previously.[7] Electromyographic studies have been normal in both twins, as have electron microscopic studies done on a muscle biopsy in one of the twins at the time of an elective surgery.

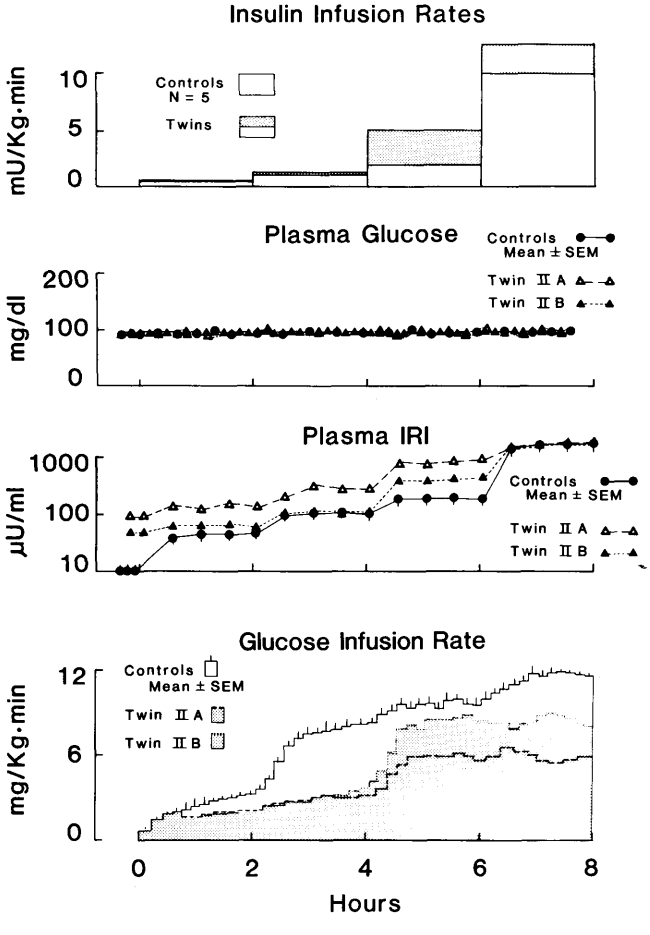

FIGURE 3. Plasma glucose and insulin concentrations, as well as glucose infusion rates, during two euglycemic clamps done on twins with acanthosis nigricans and insulin resistance. The mean results from five normal adult controls are also included.

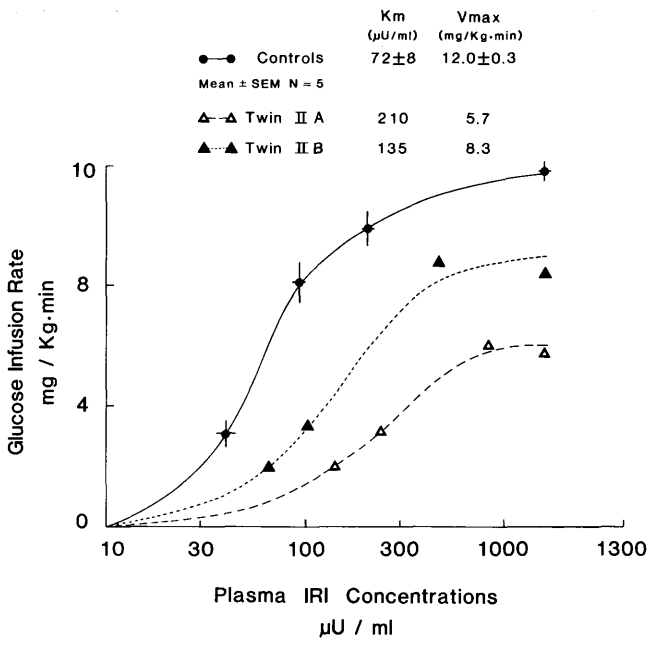

FIGURE 4. Insulin dose-response curve from euglycemic insulin clamps done on two patients with acanthosis nigricans and insulin resistance. The mean glucose infusion rates during the final 40 min of each insulin dose versus the mean plasma insulin concentrations are plotted. The patients' curves show decreased maximal effect and are shifted to the right when compared with a meaned curve for five control adults.

Of particular interest is the mild hyperprolactinemia found in the twins, which, to our knowledge, has not been previously reported in patients with type A insulin resistance, although an association between insulin resistance and hyperprolactinemia has been described in patients with markedly elevated prolactin levels.[23] The hyperprolactinemia in our patients does not at present seem to be associated with polycystic ovary disease, since the twins do not have the elevated free testosterone concentrations or elevated LH/FSH ratios typically seen in that disorder.[24,25]

In summary, type A insulin resistance is described in four affected females from one family, including identical twins. The decrease in normal insulin-stimulated glucose metabolism in the twins and the presence of normal erythrocyte and monocyte receptor binding suggest that their insulin resistance is due to a postbinding defect in insulin action.

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