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# Insulin Resistance, Skin Changes, and Virilization: A Recessively Inherited Syndrome Possibly Due to Pineal Gland Dysfunction

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*Summary.* A syndrome of glucose intolerance associated with hyperinsulinaemia and insulin resistance, skin changes, and mild virilization occurred in two daughters of a first-cousin marriage. The condition is probably inherited as an autosomal recessive trait. It is likely to represent a widespread disturbance in neuroendocrine control; the primary metabolic error may involve pineal hormone synthesis.

*Key words*: Insulin, insulin resistance, pigmentation, pineal gland, virilization.

In this report we describe, in two sisters who were daughters of a first-cousin marriage, an unusual syndrome manifested by glucose intolerance and hyperinsulinaemia, skin changes, and mild virilization, without evidence of lipodystrophy. Some of these features occur in a number of disorders, but a condition closely resembling this syndrome has been reported only twice previously: in three siblings studied by Rabson and Mendenhall [1] in 1956, and in two siblings described briefly by West and colleagues [2] in 1972. A common finding at autopsy in the four children who died was hypertrophy of the pineal gland. The apparently disparate features of this condition can best be explained in terms of a widespread disturbance in neuroendocrine control, and current evidence on the function of the pineal supports the possibility that the primary defect is in this gland [3, 4].

## Case Reports

### *Family History*

The relevant section of the pedigree is shown in Fig. 1. The parents (III.3 and III.4) of the propositi (IV.3 and IV.8) were first cousins. Both parents were healthy and of normal intelligence; no significant abnormality was found on examination, and their fasting blood glucose concentrations were normal. A paternal uncle (III.2) had died at the age of 29 years in acute diabetic ketoacidosis, and one paternal cousin had juvenile-onset diabetes.

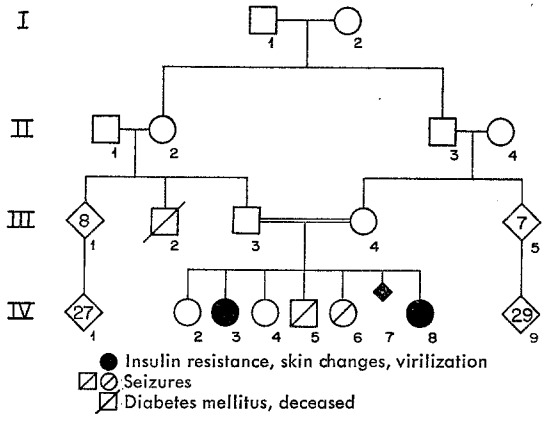


Fig. 1. Family pedigree

*Case 1.* IV.3 was an obese and hirsute infant with especially prominent fat deposition in her cheeks. In early childhood her skin was unusually dark and, in the flexures, thickened and pigmented. She had been considered tall for her age through childhood; pubertal development had started before age 9. Her general health was satisfactory. At age 12, polydipsia, polyuria, and glycosuria developed; diabetes mellitus was diagnosed and insulin treatment was started.

First Visit. At age 14, her height was 154 cm and her weight was 48 kg (25th and 50th percentiles, respectively, for American children of her age). Her general appearance and habitus were somewhat masculine, but there was ample subcutaneous fat. The skin showed the following characteristics: coarseness of the facial features; moderately severe acne over the face and shoulders; generalized darkening; acanthosis nigricans around her neck and in the axillas, antecubital areas, groin, and popliteal fossas (but no buccal pigmentation); abnormal hirsutism of her face, trunk, and limbs; and coarseness and thickening of the skin of the distal extremities. Her tongue was fissured. Her breasts were small, and pubic and axillary hair was profuse. The clitoris was slightly but definitely enlarged. The vaginal mucosa appeared anoestrogenic, and only occasional cornified epithelial cells were present in a vaginal smear. Pelvic examination revealed an infantile uterus; ovaries were impalpable. Significant results of laboratory investigations are listed in Table 1.

Doses of regular insulin up to a maximum of 700 U daily had no effect on the blood and urine glucose. Porcine insulin was also ineffective. The addition of prednisone (40 mg/day) to the regimen further increased the hyperglycaemia and glycosuria. The administration of phenformin (50 mg, three times daily) decreased slightly the amount of urinary glucose, but had no effect on the blood glucose. The combination of phenformin and regular insulin (200 U/day) did diminish the urinary glucose loss (to 25 to 80 g daily), but not the blood glucose values. When the patient was discharged she was receiving 50 U of regular insulin daily and 50 mg of phenformin three times daily.

Subsequent Visits. At age 15 years, the physical findings were unchanged. Significant results of laboratory investigations are given in Table 1. Since the last visit there had been one spontaneous episode of light vaginal bleeding lasting for 3 days. Parenteral oestrogen therapy had recently been given and, although the urinary oestrogen concentration was high (4,375 rat units/24 h), pituitary gonadotropin secretion was unsuppressed (value, 26 rat units/24 h). Shortly after this visit, therapy with insulin, phenformin, and oestrogen was discontinued; no apparent change in her condition ensued.

She was seen again when 17 years old. Since her previous visit, she had had only two light menstrual periods. A recent laparoscopy had revealed "small ovaries with multiple small cysts and a hypoplastic uterus." Her height was 158 cm and her weight, 60 kg. The physical findings were essentially unchanged. Significant results of laboratory investigations are listed in Table 1. Intravenous insulin tolerance tests (bovine and porcine insulins, 0.1 U/kg body weight) caused no significant decrease in blood glucose, and the rate of disappearance of $^{131}$I-labeled bovine insulin was comparable to that in diabetics without insulin antibodies [5].

Table 1. *Significant laboratory values, case 1*

| Variable | Time of study | | | |
|---|---|---|---|---|
| | Age 14 | Age 15 | Age 17 | Age 20 |
| Blood glucose, fasting (μg/dl) | 190—250 | 190—230 | 270 | 190—260 |
| Urine glucose (g/24 h) | 119—131 | 136 | 164<br>252 | 7.4 |
| Haemoglobin (g/dl) | 15.3 | 15.5 | 15.4 | 16.4 |
| Insulin-binding antibody (%) | 8 | | 2 | Nil |
| Plasma insulin, fasting (μU/ml) | | | 180—280 | 159 |
| Plasma cortisol, a.m./p.m. (μg/dl) | 28/16 | 23/15 | 25/10 | 38/10 |
| Urine 17-ketosteroid (mg/24 h) | 4.4 | 8.3 | 6.7<br>8.8 | 3.2 |
| Plasma growth hormone, fasting (ng/ml) | | | <2 | 6.1 |
| Plasma cholesterol (mg/dl) | 178 | | 279 | 205 |
| Plasma triglycerides (mg/dl) | 46 | | 80 | 69 |

Table 2. *Tolbutamide tolerance test, case 1*

| Time, min | Blood glucose, mg/dl | Serum insulin, μU/ml | Serum growth hormone, ng/ml |
|---|---|---|---|
| 0 | 258 | 159 | 6.1 |
| 3 | 266 | 177 | 6.1 |
| 30 | 262 | 582 | 5.7 |
| 60 | 246 | 188 | 12.0 |
| 90 | 244 | 249 | 4.7 |
| 120 | 208 | 350 | 5.8 |
| 180 | 205 | 249 | 19.8 |

By the age of 20, her condition had spontaneously improved, although no treatment had been given. Her menstrual periods were regular, her breasts had enlarged, the acne had cleared, and the pigmentation and acanthosis nigricans were less evident, and she had no symptoms except polydipsia and polyuria. There was no evidence of retinopathy or other chronic diabetic complications. Laboratory investigations showed findings listed in Table 1. The BMR was +12%. An intravenous tolbutamide test was performed; the results are shown in Table 2. No treatment was recommended.

No evidence of significant ketosis was found at any time during her course.

*Case 2.* IV.8 was abnormally hirsute but not obese. By age 3, the appearance of her skin was similar to that of her sister. She was tall for her age compared with her siblings and peers. Her general health was satisfactory.

At age 8, she was intelligent and mature for her age. Her height was 131 cm and her weight was 28 kg (in the 75th percentile for American children of her age). Her general habitus was somewhat masculine, with good muscular development, but there was ample subcutaneous fat. Her features were rather coarse, but her tongue was not fissured and there was no buccal pigmentation. Her skin was darkly pigmented, especially over pressure areas and skin creases. The striking changes of acanthosis nigricans affected all the flexures; over the extremities the skin was remarkably coarse, thickened, and hirsute and there were numerous circular, darkly pigmented scars on the shins. She showed breast budding, but no significant pubic or axillary hair growth. The clitoris was slightly enlarged, the uterus was normal for her age, and the ovaries were impalpable.

The haemoglobin concentration was 14.4 g/dl. The plasma concentrations of lipids, cortisol, luteinizing hormone, follicle-stimulating hormone, oestrogen, and testosterone and the excretion of urinary steroids were within normal limits for her age. Fasting blood glucose values were also normal (70 and 83 mg/dl) and there was no glycosuria or ketosis, but plasma insulin values were extremely high (885 and 904 μU/ml). The results of glucose and tolbutamide tolerance tests are shown in Tables 3 and 4.

## Discussion

Many inherited diseases may be associated with glucose intolerance, but the underlying mechanisms are usually obscure and the association of hyperin-

sulinaemia with insulin resistance is rare [6]. In these two sisters, resistance to insulin was the most striking metabolic abnormality.

The occurrence of such a remarkable combination of findings in two of six siblings whose parents, though unaffected, were first cousins provides strong evidence for a familial disorder inherited as an autosomal recessive trait.

Two well-documented instances of insulin resistance and acanthosis nigricans have been reported [7, 8]. The plasma of these patients had a high content of immunoreactive insulin and also a high biologic insulin-like activity; thus, the resistance seemed to be due to decreased cellular responsiveness.

Glucose intolerance may occur in at least 32 separate genetic disorders [9], but the combination of both endogenous hyperinsulinaemia and resistance to administered insulin has been demonstrated in only four such conditions: type II familial growth hormone

Table 3. *Glucose tolerance test, case 2*

| Time, min | Blood glucose, mg/dl | Serum insulin, μU/ml | Serum growth hormone, ng/ml |
|---|---|---|---|
| 0 | 70 | 885 | 5.8 |
| 60 | 177 | >1,000 | 3.8 |
| 120 | 89 | >1,000 | ... |
| 180 | 81 | 658 | 4.6 |
| 240 | 43 | 920 | 4.5 |
| 300 | 46 | 852 | 6.1 |

had no evidence of lipodystrophy and in whom insulin-resistant diabetes developed at age 7 years. They also showed a prematurely aged appearance, early dentition, hirsutism, rough thickened pigmented skin (especially in the flexures), enlarged genitalia, and mental precocity. All three died from infection and uncontrolled diabetes within 2 years of the onset of diabetes. Autopsy showed similar findings in all three, of which the most striking was hypertrophy of the pineal gland with essentially normal histologic features, enlargement of the adrenals and pancreas, and, in the two girls, follicular cysts of the ovaries. A fourth child in the family showed similar findings and died from intussusception at the age of 5 months. Another child was anencephalic. There were two normal siblings. West and colleagues [2] reported two siblings with unusual facies, enlarged and fissured tongues, advanced dentition and dental dysplasia, acanthosis nigricans, thickened nails, and enlarged external genitalia. The older sibling, a girl, showed glycosuria and ketonuria at the age of 5 years that did not respond to insulin, chlorpropamide, or metformin. Her condition deteriorated — she manifested episodes of severe ketoacidosis and recurrent infection — and she died at the age of 7 years. At autopsy the pineal gland was five times the normal size and her ovaries were cystic. Her 3-year-old brother had intermittent glycosuria and ketonuria. His serum insulin values were 556 μU/ml (fasting) and 3,208 μU/ml (after an oral dose of glucose).

Table 4. *Tolbutamide tolerance test, case 2*

| Time, min | Blood glucose, mg/dl | Serum insulin, μU/ml | Serum growth hormone, ng/ml | Serum free fatty acids, μEq/liter |
|---|---|---|---|---|
| 0 | 83 | 904 | 2.4 | 1,157 |
| 3 | 74 | 806 | 20.1 | 1,354 |
| 30 | 55 | >1,000 | 14.7 | 1,362 |
| 60 | 39 | >1,000 | 7.6 | 2,365 |
| 90 | 51 | 658 | 13.9 | 2,470 |
| 120 | 44 | 303 | 10.9 | 2,260 |
| 150 | 46 | 943 | 19.4 | 2,037 |
| 180 | 42 | 289 | 17.2 | 1,929 |

deficiency [10], ataxia telangiectasia [11], Werner's syndrome [12], and lipoatrophic diabetes [13]. Our two patients showed few other features in common with those of the first three conditions, but a number of striking similarities to lipoatrophic diabetes were apparent despite the lack of abnormality in fat distribution and serum lipids in our patients.

There are two previous reports of cases that resemble the present cases perhaps even more closely, although those patients seem to have had a more severe metabolic disturbance with recurrent ketosis and susceptibility to infection leading to early death. Rabson and Mendenhall [1] described three children (two girls and a boy, of normal, unrelated parents) who

The cause of the insulin resistance in these conditions is obscure; because neither antibody formation nor other recognized factors can be implicated, different mechanisms must be sought. Experimental lesions of the hypothalamus affect hepatic glycogenolysis and the secretion of insulin and glucagon, but the response to exogenous insulin is unaltered [14, 15]. The hypothalamic-pituitary axis may, however, also affect carbohydrate metabolism by producing a humoral insulin-antagonist that differs from other recognized pituitary hormones [16—18]. The metabolic effects closely resemble those seen in our patients.

Other clinical features of our patients also suggest a possible underlying disturbance of the hypothalamic-

pituitary axis. The generalized melanotic pigmentation and the pigmentation of scars may be mediated by secretion of melanocyte-stimulating hormone [19]. Benign acanthosis nigricans is associated with a number of disorders in which a common factor is primary or secondary alteration in hypothalamic-pituitary function [20]. There was little evidence of increased ACTH secretion in our patients. The older child showed a transient increase in the excretion of urinary 17-ketosteroids but 17-ketogenic steroid excretion and plasma cortisol values were normal, which is consistent with the clinical findings of mild virilization without evidence of glucocorticoid excess. The coarse facial features and thickening of the skin of the extremities in both sisters resembled the soft-tissue changes seen in acromegaly, and the values for serum growth hormone were consistent with a modest increase in secretion of this hormone. Abnormality of gonadotropin secretion was suggested by the fact that, in spite of the virilization, isosexual maturation started at a relatively early age in both sisters; further evidence comprised the observations that, in the older child, gonadotropin secretion was not suppressed by a high level of exogenously administered oestrogen and that she had polycystic ovaries.

It is difficult to postulate a single metabolic abnormality involving either the hypothalamus or the pituitary that could lead to such widespread disturbance of humoral function; hence the possibility that the primary defect may lie in the pineal gland. No abnormality of the pineal has been noted in lipoatrophic diabetes. Our patients do resemble the four children with pineal enlargement described by Rabson and Mendenhall [1] and by West and colleagues [2]. A block in pineal hormone synthesis due to absence or deficiency of an enzyme would be most likely to result in a dominant picture of pineal underactivity [3, 4, 21—25]. Because several hormones are produced, a mixed picture of underactivity and overactivity, as in disorders of adrenal steroid biosynthesis, might also occur with or without hypertrophy of the gland. The similarities and differences among apparently related disorders might result from such factors.

It seems probable, therefore, that the primary metabolic defect in the syndrome described is an inborn error of pineal hormone metabolism, and that the multiple manifestations result from disturbance of the normal controlling influence of this gland on neuroendocrine function.

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