Familial insulin-resistant diabetes, multiple somatic anomalies, and pineal hyperplasia

R. J. WEST, J. K. LLOYD, and W. M. L. TURNER

From the Department of Child Health, Institute of Child Health, London, and the Paediatric Department, Burnley General Hospital, Burnley

West, R. J., Lloyd, J. K., and Turner, W. M. L. (1975). Archives of Disease in Childhood, 50, 703. Familial insulin-resistant diabetes, multiple somatic anomalies, and pineal hyperplasia. A syndrome comprising unusual facies, dry skin, acanthosis nigricans, thickened nails, hirsutism, dental precocity and dysplasia, abdominal protuberance, and phallic enlargement is described in 2 sibs. Both have developed diabetic ketoacidosis with insulin resistance. The elder child, a girl, had recurrent septic episodes and died at the age of 7·8 years. At necropsy the pineal gland was hyperplastic, weighing 900 mg. Investigation of the younger sib over a 4-year period has shown decreasing glucose tolerance, and he was frankly diabetic with ketoacidosis by the age of 6·8 years. Serum insulin concentrations have always been grossly raised. Though the mechanism for insulin resistance has not been definitely established, a functional abnormality of the hypothalamus or pituitary is postulated to explain the many endocrine features of the syndrome.

The role of the pineal gland in human metabolism is uncertain; a syndrome in which pineal hyperplasia appears to be an integral part may help to elucidate its function. Such a syndrome was reported by Rabson and Mendenhall (1956) who described 3 sibs who initially presented with dental and skin abnormalities, abdominal distension, and phallic enlargement. Insulin-resistant diabetes developed, and the patients died of ketoacidosis and intercurrent infection during childhood. At necropsy pineal hyperplasia was found in all 3 children. 5 other children described in published reports had similar features (Mason and Sly, 1937; Wiedermann et al., 1968; Barnes et al., 1974), but biochemical details are limited. This report records two further examples of the syndrome, and speculates on the role of the pineal gland in this disorder.

Case reports

Case 1. A girl, the first child of healthy unrelated parents, was born at term after an uneventful pregnancy, weighing 2 kg. Unusual facies and abdominal distension were noted from birth. Primary dentition started at 3 months, and was complete by 1·2 years. Secondary dentition started at the age of 3·5 years and the teeth were clearly abnormal in appearance. Thickened finger and toe nails were present from infancy. Developmental progress was normal.

Throughout childhood she had a good appetite but appeared more thirsty than other children. At the age of 5, during a routine medical examination, she was found to have glycosuria with ketonuria, and was admitted to hospital. On admission height and weight were both well below the 3rd centile, but she did not appear acutely ill. She was noted to have unusual facies, hirsutism, dry skin with acanthosis nigricans of neck and axilla, thickened nails, dysplastic and carious teeth with greatly advanced dental age (Fig. 1), and a deeply fissured tongue. Her abdomen was markedly protuberant and the clitoris was large but there was no evident organomegaly or pubic or axillary hair.

Investigation showed a fasting blood sugar of 155 mg/100 ml and treatment of her diabetes mellitus was started with soluble insulin, the dose being gradually increased to 300 IU daily, without any improvement of ketonuria, polyuria, or lowering of blood sugar. Insulin antibodies could not be detected. The sequential addition of prednisone, chlorpropamide, and metformin to the insulin therapy did not favourably influence the hyperglycaemia, and accordingly all anti-diabetic therapy was discontinued.

Over the next 2 years she remained hyperglycaemic and ketotic, and her general health gradually deteriorated. She lost weight, had several episodes of dental sepsis, and on one occasion ketoacidosis with semi-coma required treatment with intravenous fluids.

Received 20 January 1975.
At the age of 6·8 years she was admitted to The Hospital for Sick Children, London, for further study. On examination she weighed 11·5 kg and was grossly wasted, with no apparent subcutaneous fat. The somatic features were as already described and her dental age was assessed at around 12 years. Investigations showed Hb 14·5 g/100 ml, WBC 12 900/mm³ with 70% neutrophils. Serum sodium was 119 mEq/l, potassium 2·7 mEq/l, chloride 97 mEq/l, bicarbonate 9 mmol/l, and urea 26 mg/100 ml. Fasting blood glucose was 235 mg/100 ml, plasma calcium 8·0 mg/100 ml, inorganic phosphorous 1·3 mg/100 ml, alkaline phosphatase 38 KA units, and total serum protein 6·8 g/100 ml. Serum transaminases were normal. Urine volumes varied between 5–6 l daily, and contained 100–200 g glucose, and about 90 mEq sodium and 45 mEq potassium. There was a generalized amino-aciduria. Chest x-ray was normal, the bones were somewhat porotic and bone age was 5 years. Barium meal showed widening of the jejunum with coarse mucosal folds. Faecal fat was 4·5 g/day (mean of 5 days). Results of special investigations are given separately.

The electrolyte abnormality was treated with sodium bicarbonate and potassium supplements, and serum values gradually returned to normal, as did plasma calcium and inorganic phosphorus; the aminoaciduria improved. Insulin, both beef and pork, was given in doses up to a total of 1000 IU daily without apparent effect and the subsequent addition of metformin 1·5 g/day was also without effect. Trials of fructose and xylitol as alternative dietary carbohydrate were without benefit. She was discharged on electrolyte and alkali supplements only. Subsequent progress was complicated by episodes of infection, including otitis media, dental abscess, pneumonia, and ischiorectal abscess. At the age of 7·8 years she died at home after a short diarrhoeal illness.

**Post-mortem examination** showed distension of the whole of the small intestine, and of the ascending colon. There was a small amount of peritoneal fluid. The liver was slightly enlarged. Spleen, pancreas, adrenals, and kidneys appeared normal. The ovaries were enlarged and somewhat cystic, but the uterus and adnexa were normal. The appearance of the brain was normal and the pituitary gland was of normal size. The pineal gland was grossly enlarged, weighing 900 mg (normal <150 mg). On microscopical examination, the pancreas showed conspicuous hyalinization of the islets. The adrenals showed well-marked compact cell change. The ovaries were histologically normal, as were sections of myocardium, skeletal muscle, brain, stomach, jejunum, caecum, spleen, thyroid, and uterus. The lungs showed alveolar congestion, and in the liver there was some vacuolation of the parenchymal cells and dilatation of the sinusoids. There was hyalinization of some of the afferent arterioles of the kidney. The pituitary was normal in size, with normal proportions of the various cell types. The pineal, though enlarged, showed no histological abnormalities (Fig. 2).

**Case 2.** A boy, the brother of Case 1, was born at term weighing 2·3 kg. His facial appearance was similar to his sister's; primary dentition started at 4 months and secondary dentition at 3 years. Roughness of the skin was noted at the age of 9 months and thickened nails at 1·5 years. In view of the similarity to his sister he was investigated at The Hospital for Sick Children at the age of 3·1 years.

On examination the facial resemblance to his sister was obvious (Fig. 3). He was, however, well nourished, with both height and weight between the 3rd and 10th centiles. His skin was dry, moderately hirsute, and with acanthosis nigricans of neck, axillae, and cubital fossae. The nails were thickened, the teeth were dysplastic and carious, and the dental age advanced. The tongue was fissured, the abdomen was somewhat protuberant, and there was penile enlargement but no pubic hair or testicular enlargement. Urine analysis showed occasional glycosuria, but there was no polyuria or polydypsia, and hyperglycaemia could not be shown. Results of special investigations are given later.

When reviewed at the age of 4·9 years his clinical condition was essentially unchanged. By 6·8 years, however, he had developed increased thirst and polyuria though he remained well nourished. His dental age was around 14 years. Urine volume varied between 3–4 l daily, and contained approximately 200 g glucose/24 h. Fasting blood glucose varied between 200 and 260 mg/100 ml. He was ketonuric and mildly hypokalaemic, but was not acidotic. Hypokalaemia was corrected by oral potassium supplements but neither insulin nor oral hypoglycaemic drugs have been used.

At the time of writing he was 7·5 years old; there has been no major clinical progression of his disease.
**Special investigations**

**Glucose tolerance tests.** Glucose tolerance tests (GTT), using oral glucose (1.75 g/kg body weight to a maximum of 50 g) and measuring blood glucose and serum insulin at 0, 30, 60, 90, 120, and 150 minutes, were performed on both children and their parents; plasma nonesterified fatty acids (NEFA) were measured in most tests. Glucose was measured on venous blood by an autoanalyser glucose oxidase method, serum insulin by a double binding radioimmunoassay, and plasma NEFA by the method of Fosbrooke and Tamir (1968). In Case 1 the test was done at the age of 7.3 years, 2 months after discontinuing insulin therapy. In Case 2, tests were performed at 3.1, 4.9, and 6.8 years.

Measurement of serum insulin in Case 1 was complicated by the presence of antibody, presumably induced by exogenous insulin. Fractionation of two of the serum samples through a G100 Sephadex column removed the antibody and enabled an approximate result to be obtained. In Case 2 antibodies were not present in the serum. The results of the GTTs are shown in the Table. In Case 1 there was marked hyperglycaemia throughout the test, and serum insulin at 0 and 60 minutes was high; the response of plasma NEFA was normal. In Case 2 the first GTT showed normal glucose tolerance, but extremely high serum insulin con-
concentrations. The second and third tests showed progressively impaired glucose tolerance; in the third test serum insulin values were still markedly raised though somewhat lower than previously. Plasma NEFA response was normal in the two tests where it was measured.

The mother had normal glucose tolerance but somewhat raised serum insulin values throughout the test. The interpretation of these results is hampered by the fact that she was at the time taking Ovulen 50 (Searle) for contraceptive purposes; it seems unlikely, however, that this drug was the sole cause of the hyperinsulinaemia (Wynn and Doar, 1969). The father had a normal response to oral glucose for all 3 variables measured (Table).

**Investigation of insulin resistance.** Investigation of Case 1 was hampered by the presence of antibodies and the very poor clinical condition with evidence of many secondary metabolic abnormalities. Most investigations have therefore been carried out on Case 2 who never received exogenous insulin and whose general clinical state was good at the time of testing. Measurement of his serum insulin by radioimmunoassay has always shown grossly raised values, and no antibody or proinsulin has been detected on any occasion. Bioassay of serum insulin, using isolated fat cells (Dr. O. Sovik) gave a value of 5133 μU/ml, compared with immunoreactive serum insulin of 5850 μU/ml on the same sample. Insulin activity in this sample was completely suppressed by insulin antibody. Gel filtration of serum yielded a single insulin peak with mobility identical with crystalline insulin (Dr. O. Sovik). These investigations therefore failed to show any abnormality of structure of the serum insulin. Measurement of insulin binding of lymphocytes (Dr. N. Lazarus) gave values within the range obtained for obese adults (normal data for children not available).

The possibility of hormonal antagonism to the action of insulin has been investigated in both children. Serum cortisol in Case 1 was normal (9 a.m. cortisol 14·0 μg/100 ml; normal 17·3 ± 7·8 μg/100 ml, mean ± 1 SD). In Case 2 the cortisol level was sometimes high, the values being 13·4, 28·0, and 28·5 μg/100 ml for 9 a.m., and 9·6 μg/100 ml at midnight (normal 3·1 ± 1·2 μg/100 ml, mean ± 1 SD). Cortisol production rate (isotopic dilution) in Case 2 was also raised at 23·2 mg/m² per 24 h (normal 12·3 ± 2·8, mean ± 1 SD), though urinary cortisol excretion, measured at about the same time was 0·8 mg/24 h (normal for age 0·4-3·2 mg/24 h, Dr. C. Forsyth).

Plasma growth hormone in Case 1 in the fasting state was 7 μU/ml, and in Case 2 varied between 3·3 and 6·2 μU/ml (3 estimations). In Case 2 the response to oral Bovril (Jackson, Grant, and Clayton, 1968) was subnormal with a maximum value of 8·2 μU/ml (normal rise of at least 7 μU/ml).

---

**TABLE**

Results of oral glucose tolerance tests in patients and parents

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Glucose (mg/100 ml)</th>
<th>Insulin (μU/ml)*</th>
<th>NEFA (mEq/l)</th>
<th>Minutes after glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Case 1</td>
<td>7·3</td>
<td>265</td>
<td>212</td>
<td>1·56</td>
<td>0·70</td>
</tr>
<tr>
<td></td>
<td>3·1</td>
<td>42</td>
<td>550</td>
<td>1·98</td>
<td>1·93</td>
</tr>
<tr>
<td>Case 2</td>
<td>4·9</td>
<td>90</td>
<td>1050</td>
<td>0·88</td>
<td>0·50</td>
</tr>
<tr>
<td></td>
<td>6·8</td>
<td>259</td>
<td>498</td>
<td>460</td>
<td>535</td>
</tr>
<tr>
<td>Mother</td>
<td>30</td>
<td>61</td>
<td>48</td>
<td>101</td>
<td>310</td>
</tr>
<tr>
<td></td>
<td>Glucose (mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>32</td>
<td>78</td>
<td>16</td>
<td>128</td>
<td>130</td>
</tr>
</tbody>
</table>

*After removal of circulating antibody.
NEFA, plasma nonesterified fatty acids.

---

10.1136/adc.50.9.703 on 1 September 1975. Downloaded from http://adc.bmj.com/
however, on one occasion during a GTT a growth hormone level of >40 μU/ml was recorded.

Plasma glucagon (Dr. S. Bloom) in Case 2 at a time when he was hyperglycaemic (blood glucose 300 mg/100 ml) was 97 pg/ml (normal adults 10–59 pg/ml). No direct estimations of catecholamines were made; urinary VMA in Case 2 was 1.9 mg/24 h (normal up to 3.3 mg/24 h).

**Other endocrine investigations.** In Case 1 protein-bound iodine was 5 μg/100 ml (normal 2.5–6.6 μg/100 ml). Urinary ketosteroid excretion was 2.6 mg/24 h, and hydroxycorticoid excretion was 7.4 mg/24 h (both mean of 3; normal ketosteroids 1.4 ± 0.7, mean ± ISD, hydroxycorticoids 0.6–6.4 mg/24 h).

In Case 2 it was possible to assay a number of pituitary hormones in addition to growth hormone; normal results were obtained for serum thyroid stimulating hormone (1.8 μU/ml, Dr. B. Ormston), ACTH (9 a.m. 33 pg/ml, midnight <12 pg/ml, Dr. L. Rees), FSH (<16 pg/ml, Dr. L. Rees), and prolactin (11.2 ng/ml). Urinary leutinizing hormone was raised at 9.5 IU/24 h (mean of 2; normal 1.37 ± 0.45 IU/24 h mean ± ISD); urinary follicle stimulating hormone was <0.5 IU (mean of 3; normal <1 IU/24 h).

Serum thyroxine was normal (9.3 and 6.9 μg/100 ml), as was plasma testosterone (Dr. B. Rudd). Urinary 17-ketosteroids at age 4–9 years were 2.9 mg/24 h (normal for age 0.8 ± 0.5, mean ± 1 SD), and at age 6–9 were 2.8 mg/24 h (normal for age 1.4 ± 0.7 mg/24 h). Urinary dehydroepiandrosterone (Dr. C. Forsyth) was high at 37 μg/24 h (normal for age up to 18 μg/24 h), whereas aetiocholanolone, androsterone, 11-deoxy-17-ketosteroids, and corticosterone excretions were normal.

**Investigation of pineal gland.** An attempt to study the pineal gland was made in Case 2. An EMI scan of the brain at the age of 7 years showed a normal sized pineal and there was no distortion or enlargement of the ventricular system. Urinary 5-hydroxy-indole-acetic acid (formed during melatonin synthesis) excretion was not raised (Dr. K. Blau). Administration of oral melatonin in dosage up to 200 mg/day for 12 days did not improve the diabetic state (Fig. 4), though the recognized side effects of drowsiness and slurring of speech occurred.

**Discussion**

Our patients most closely resemble the family reported by Rabson and Mendenhall (1956) and the patient of Mason and Sly (1937). From these 6 patients the characteristic features of the syndrome appear to be low birthweight, dry skin, thickened nails, hirsutism, acanthosis nigricans, dental precocity and dysplasia, abdominal protuberance, phallic enlargement, and insulin-resistant diabetes mellitus with ketosis developing during childhood, and association with frequent septic episodes. All 3 children described by Rabson and Mendenhall (1956) and Case 1 of our family died in mid-childhood, necropsy showing marked pineal hyperplasia. No follow-up of the patient of Mason and Sly (1937) is available after the age of 2 years.

The brother and sister described by Wiedemann et al. (1968) did not have abdominal distension or phallic enlargement, and were still living at the ages of 13 and 11, respectively; the 2 sisters described by Barnes et al. (1974) did not have abnormal teeth or nails, and are surviving at the ages of 23 and 11 years. However, as both these sibships have many similarities to the other 6 patients, they may represent less severe variants of the syndrome.

The syndrome appears to show autosomal recessive inheritance, and the 2 sisters described by Barnes et al. (1974) were daughters of a first-cousin marriage. The raised serum insulin found in the mother of our patients may be a biochemical indication of her heterozygous status.

The mechanism of the insulin resistance has not yet been established. Insulin antibodies were not present in Case 2, or initially in Case 1. Growth hormone, cortisol, glucagon, and adrenaline were not present in amounts likely to cause insulin resistance. Suppression of plasma NEFA by oral glucose in both our patients suggested that adipose tissue at least was not totally resistant to the action of insulin. Nevertheless, some form of tissue resistance cannot be completely excluded.

The role of the pineal gland in this syndrome can
failure of pineal hyperplasia might be explained by mechanisms attempting to inhibit this FSH. The failure to show pineal hyperplasia in our second patient may be due to the limitations of EMI scanning, or may simply reflect the stage of his disease. Serial studies are clearly indicated.

A unifying hypothesis to explain all the somatic and metabolic features in this syndrome is not yet possible. The extremely high circulating insulin concentrations present from an early age may possibly play some part in the development of the dental, skin, and nail abnormalities.

We thank Dr. Helen Blyth for drawing our attention to the report by Rabson and Mendenhall; Mrs. Doreen Jackson and the other staff of the Department of Chemical Pathology, The Hospital for Sick Children, for many endocrine estimations; all those mentioned in the text for special investigations; and the many clinical colleagues with whom we had helpful discussion.

References


Correspondence to Dr. R. J. West, Department of Child Health, St. George's Hospital, Blackshaw Road, Tooting, London SW17.