Transient Neonatal Diabetes Mellitus in Sibs

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Ferguson, A. W., and Milner, R. D. G. (1970), *Archives of Disease in Childhood*, 45, 80. Transient neonatal diabetes mellitus in sibs. The occurrence of transient neonatal diabetes mellitus in successive male sibs is described. Both infants were small in relation to their periods of gestation and the placentas were abnormal. Subsequent investigation of the mother revealed a flat glucose tolerance curve with normal plasma insulin levels. Transient neonatal diabetes mellitus may be due to delayed maturation of fetal β -cells caused by a combination of maternal and placental factors.

The clinical syndrome described as 'transient neonatal diabetes mellitus' or 'idiopathic neonatal hyperglycaemia' has become more widely known since Hutchison and his colleagues (1962) described 4 cases and reviewed 8 which had been recorded previously. Since then further case reports have occurred sporadically. The pathological basis of the condition remains obscure, though a prominent feature is that affected infants are usually small for their gestational age.

Two cases are presented here because the condition has not previously been reported in sibs.

Case Histories

These brothers were the first and second-born children of healthy, unrelated parents. Both infants developed all the features of transient neonatal diabetes mellitus. The diagnosis was made much earlier in the second infant because the condition was anticipated. Both infants were small in relation to the period of gestation and in both cases the placenta was small and infarcted.

Case 1. This male infant was born on 14 November 1963 at 42 weeks gestation, birthweight 2155 g. The mother, aged 21 years, had a normal pregnancy with no toxæmia, and labour was induced surgically because of fetal postmaturity. During the second stage there was meconium-stained liquor and slowing of the fetal heart during uterine contractions. After an episiotomy the infant was born by spontaneous vertex delivery. He was limp and blue but cried immediately. Regular respirations were established at 5 minutes. The placenta was grossly infarcted and calcified, but was not weighed.

The infant was breast-fed and sucked well. However, he failed to gain weight, and on the 15th day began to vomit occasionally. On the 19th day he was transferred to the Children's Ward for further investigation. He then weighed 2065 g., was marasmic, wide-eyed and thirsty, with a rectal temperature of 39.4 °C (Fig.). Blood sugar, 720 mg./100 ml.; CSF sugar, 405 mg./100 ml.; CSF protein, chloride, and cell count normal; blood urea, 77 mg./100 ml.; urine contained 2% sugar but no ketones.

A subcutaneous infusion of 1/5 normal saline was given. All urine voided was collected and tested for sugar and acetone. Soluble insulin was given two or three times daily in doses ranging from 2 to 6 units.

Ketones were never found in the urine. Administered insulin totalled 12 units daily for most of the first fortnight, but thereafter the dose gradually fell. No attempt was made to keep the urine entirely sugar-free because of the particular dangers of hypoglycaemia in infancy. However, at 5 weeks a brief hypoglycaemic convulsion occurred which was terminated by intravenous glucose. From the start of treatment there was immediate clinical improvement and a steady gain in weight.

At 6 weeks intermittent vomiting, abdominal distension, fever, and diarrhoea developed, associated on three occasions (2, 3, and 6 January 1964) with serum potassium over 7 mEq/l., and with low sodium and chloride levels. On these dates blood sugar levels of 550, 770, and 60 mg./100 ml. were recorded. The 24-hour urinary 17-oxosteroid and total oxogenic steroid excretion (5-6 January) were 0.15 and 0.64 mg. respectively. Blood urea was 30 mg./100 ml. and blood culture was negative. There was a tachycardia of 200/min., and the systolic blood pressure in the arm by the flush technique was 75 mm. Hg. Adrenal insufficiency was suspected and desoxycorticosterone acetate 1 mg. daily and subcutaneous 1/5 normal saline were administered from 7-10 January. Rapid clinical

FIG.—Case 1 aged 19 days when neonatal diabetes mellitus was diagnosed.

and biochemical recovery occurred and there was no subsequent similar relapse.

By 15 weeks when he was discharged weighing 4.25 kg. his insulin requirements had stabilized at 2 U/day, and 2 days later insulin was discontinued entirely. During the first 3 weeks at home, sugar was found in the urine in only 3 out of 105 tests. Three random blood sugar measurements in the fourth and fifth months were below 110 mg./100 ml. At 8 months he weighed 9 kg. and his physical and mental development were normal. A glucose tolerance test at age 7 months gave the following blood sugar levels (mg./100 ml.): fasting 76; 30 min., 176; 60 min., 128; 90 min., 120; 120 min., 110; 180 min., 128. Subsequent physical and mental progress was normal, and at 2 years he weighed 13.7 kg.

Case 2. This male infant was born on 5 September 1965, at 40 weeks' gestation, birthweight 2360 g. The pregnancy was uneventful, with no toxæmia or hypertension. A spontaneous vertex delivery followed an episiotomy for fetal distress and meconium-stained liquor. The infant cried immediately. The placenta was described as 'very small and gritty'. The duration of labour was: first stage, 14 hr.; second stage, 1 hr.; third stage, 10 min.

Because his brother had had transient neonatal diabetes mellitus, daily urine sugar tests were performed. These were positive from the third day, and on the fifth day the blood sugar level was 650 mg./100 ml. The infant was then transferred to the Children's Ward, where he was noted to be thin and pale with a dry tongue, but a vigorous cry. 8 units of soluble insulin were given intramuscularly at 3.30 p.m., and 1/5 normal saline was infused intravenously. At 5 p.m. the blood sugar was 518 mg./100 ml.; serum sodium, 123 mEq/l.; potassium, 7.4 mEq/l.; chloride, 116 mEq/l.; blood urea, 82 mg./100 ml. By 10 p.m. the blood sugar had fallen to 225 mg./100 ml., and by 10 a.m. the following morning it was 49 mg./100 ml. Whenever possible, urine sugar tests were done before each feed and 2–4 units soluble insulin were given if the urine contained 0.75% or more sugar. Feeds of

normally reconstituted evaporated cow's milk without added sugar were taken well, and the intravenous infusion was stopped after 24 hours. Blood sugar tests at random times, daily for the first week and subsequently twice weekly, tended to be over 300 mg./100 ml. The usual daily total of administered soluble insulin was 8 units during the first month of treatment. A hypoglycaemic episode with convulsive movements and a negative 'Dextrostix' test on capillary blood occurred at 8 weeks, but was terminated by 5 ml. 50% glucose intravenously. Thereafter, a gradual reduction in the daily dose of insulin was possible, reaching 2 units when the baby was 12 weeks old. After the age of 14 weeks no further insulin was given and all urine tests remained negative until the baby was allowed home aged 15 weeks. He continued to thrive and there was no recurrence of glycosuria. At 10 months he weighed 8.6 kg. and a glucose tolerance test gave the following blood sugar levels (mg./100 ml.) fasting, 85; 30 min., 95; 60 min., 84; 90 min., 75; 120 min., 73; 150 min., 74. At the age of 18 months physical and mental development was normal.

The mother was a healthy young woman of 1.75 m. height who tended to be plump. In neither pregnancy did she have significant albuminuria, oedema, or hypertension. Because of the experience with her first baby, she was given a glucose tolerance test early in her second pregnancy with the following results (blood sugar, mg./100 ml.): fasting, 80; 2 hr., 110; 3 hr., 116; 4 hr., 95; 5 hr., 85; 6 hr., 85. After her second child also had temporary neonatal diabetes mellitus a further glucose tolerance with plasma insulin determinations (Hales and Randle, 1963) was performed 16 months after birth (see Table). No abnormality of plasma insulin in response to oral glucose was detected, but the glucose curve was 'flat'.

Discussion

There is a striking uniformity in the clinical pattern of transient neonatal diabetes mellitus. The affected infants are small for their gestational age and have a poor placenta. At the onset of the

TABLE
Blood Sugar and Plasma Insulin Levels during Oral Glucose Tolerance Test in Mother of Brothers who had Temporary Neonatal Diabetes Mellitus*

Time After Oral Glucose (min.)	Plasma Insulin (μ U/ml.)	Blood Sugar (mg./100 ml.)
0	20	85
30	111	95
60	90	84
90	26	75
120	24	73
150	34	74

*The test was performed 16 months after the delivery of the mother's second child.

illness they have failed to gain weight and have hyperglycaemia with glycosuria but no ketonuria. Low doses of insulin are effective and after a time spontaneous regression of the diabetes occurs. The present cases conformed to this picture and being the first sibs to be reported with the condition, they lend emphasis to the viewpoint that some aspect of intrauterine life is important in the genesis of the diabetes.

Hypoinsulinism due to a delay in the development of the endocrine pancreas was suggested as an explanation for transient neonatal diabetes by Gerrard and Chin (1962). The concept was based on the hypothesis that fluctuations in fetal blood glucose levels are necessary for the normal functional development of the β -cell and the discovery that the mother of their case had persistently low blood glucose levels. There is good evidence in favour of the corollary: babies born to diabetic mothers, who have large fluctuations in blood sugar levels, have hypertrophy and hyperplasia of the pancreatic islets (Cardell, 1953) and hyperinsulinism (Baird and Farquhar, 1962). It may be relevant, therefore, that the mother of the present cases also had a flat glucose tolerance curve (Table).

The evidence for hypoinsulinism postnatally, however, is scanty, though the effectiveness of small doses of exogenous insulin possibly favours the concept. There is only one report* of a systematic study of plasma insulin levels in a baby with transient diabetes mellitus (Ferguson, 1967). In this infant intravenous tolbutamide was followed by a rise in plasma insulin and a fall in blood glucose levels, demonstrating the ability of the pancreas to release insulin and of the tissues to respond to it. There was also a rise in plasma insulin levels in response to oral glucose, but the glucose tolerance was diabetic. Those results could be interpreted as having indicated insensitivity of the

β -cell to glucose, but provided no evidence of insulin antagonism.

The idea that insulin antagonism, due to the transplacental passage of antibodies, could cause transient neonatal diabetes was put forward by Scott (1966). The suggestion rested on the fact that passively acquired maternal antibodies persist in the newborn for approximately 12–16 weeks, a period similar to the common duration of transient neonatal diabetes. Direct evidence of such a mechanism is lacking, however, and, furthermore, infants of mothers with diabetes mellitus do not get temporary diabetes, though many of them receive maternal insulin antibodies transplacentally (Spellacy and Goetz, 1963).

The fact that a large majority of the reported cases are small for their gestational ages and have a poor placenta is striking. The placenta is an important source of fetal steroids and there is both *in vitro* and *in vivo* evidence that steroids play a role in the development of the fetal endocrine pancreas.

Differentiation of the β -cells of fetal rat pancreas grown in organ culture occurred only if the tissue was incubated in the presence of fetal rat adrenal cortex (Zagury, 1959). Murrell (1966) cultured fetal rat pancreas in a medium containing hydrocortisone, and found that the tissue developed aldehyde fuchsin-positive cells, granulated β -cells, but no pancreatic acini. The insulin content of the explanted pancreas was greater than that of tissue which had developed *in utero* (Murrell, Morgan, and Lazarow, 1966).

Precocious development of rabbit fetal exocrine and endocrine pancreas was noted when cortisone or ACTH was administered to pregnant rabbits (Lee and Ring, 1956). If steroids are necessary for the normal development of the human β -cell placental insufficiency could impair insulin secretion *in utero* either directly or by an effect on the fetal adrenal cortex. It is of interest that Case 1 had one episode when he showed some clinical and biochemical features of adrenal hypofunction which responded promptly to treatment.

From the available evidence it seems likely that transient neonatal diabetes mellitus is due to delayed maturation of fetal β -cells. The delay may be caused by a combination of maternal and placental factors. First, a relatively non-fluctuating maternal blood sugar level might deprive the fetal β -cell of a stimulus to development (Gerrard and Chin, 1962). Secondly, poor placental function may contribute to delayed β -cell maturation through a deficiency of steroid hormone production.

With the present emphasis on the screening of small-for-dates babies to detect hypoglycaemia,

* See addendum.

more early cases of transient neonatal diabetes may come to light. Once diagnosed, it is desirable to investigate cases, before treatment begins, by a glucose tolerance test incorporating measurements of plasma insulin levels. When a number of infants have been so studied the roles of insulin deficiency and antagonism in the condition may become clearer.

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Addendum

Since this paper was submitted for publication, low pretreatment plasma insulin levels have been reported by Gentz in 2 affected infants.

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