

A new type of transient diabetes mellitus of infancy?

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SUMMARY Two male siblings with transient diabetes mellitus were of normal birth weight, were asymptomatic, and did not require treatment with insulin. This may be a previously undescribed disorder or part of the range of transient diabetes mellitus of infancy. Previously reported infants with transient diabetes mellitus of infancy have usually been small for gestational age and have presented with glycosuric dehydration, infections, or growth failure. Insulin concentrations after oral glucose challenge showed inadequate insulin secretion with respect to the degree of hyperglycaemia in these children. Autosomal dominant inheritance may occur in some families with this disorder, and parents of some affected children may also have had asymptomatic or unrecognised transient diabetes mellitus of infancy. Leucocyte histocompatibility antigen typing of this family did not show any association of specific antigens with transient diabetes mellitus of infancy in the affected children.

Transient diabetes mellitus of infancy is a disorder of carbohydrate metabolism of unknown aetiology. The majority of cases reported have been small for gestational age term infants presenting in the first 6 weeks of life with glycosuric dehydration, infections, or growth failure. Reports of affected siblings have been few. There have been reports of three brothers with symptomatic transient diabetes mellitus of infancy^{1 2} and three affected half siblings.^{3 4} This report is of two brothers with transient diabetes mellitus of infancy who were not small for gestational age and who had an asymptomatic course without the need for treatment with insulin.

Case histories

The subjects of this report are the only children of physically healthy, unrelated parents. Their mother, aged 26 at the time of the first delivery, is a mildly mentally retarded woman who suffers from recurrent depression and has some schizophrenic traits. Their father, who is one year younger than their mother, is illiterate and prone to physically violent outbursts. The paternal grandmother had died at the age of 26 from uncontrolled insulin dependent diabetes mellitus.

Case 1. This boy was born at 39 weeks' gestation after an uneventful pregnancy during which the only drug taken was ferrous gluconate. No glycosuria was detected during the pregnancy. Delivery was by

caesarean section because of fetal distress, and his Apgar scores were 8 at one minute and 10 at five minutes. He weighed 2940 g at birth; the placenta was normal and weighed 520 g. He was fed a cow's milk formula from birth. Blood glucose estimations performed on days 1 and 3 of life because he was jittery were normal.

Concern regarding his mother's ability to manage him led to his attendance at 11 weeks of age for a medical examination. He was thriving and developing normally. A routine urinalysis showed glycosuria, and the result of a random test of blood glucose concentration was 15 mmol/l (270 mg/100 ml). During admission for investigation it was noted that he required his wet nappies to be changed at least hourly.

Treatment with insulin was not considered necessary as he continued to grow along the 90th percentile for height and weight. He had persisting hyperglycaemia (blood glucose concentrations ranging from 14.0 to 20.4 mmol/l (252–368 mg/100 ml)) and glycosuria until the age of 5 months when his blood glucose concentrations returned to normal. He has remained normoglycaemic and has continued to thrive and develop normally, his most recent assessment being at the age of 3½.

Case 2. The brother of case 1 was born at term weighing 3140 g. The pregnancy had been uncomplicated, and the only drug taken was ferrous gluconate. No glycosuria was detected during the preg-

nancy. Delivery was by elective caesarean section and initially he required intermittent positive pressure ventilation through a face mask. His Apgar scores were 4 at one minute and 7 at five minutes. The placenta weighed 750 g and had a gritty maternal surface but was otherwise normal. Breast feeding was begun, but at 6 hours of age he was noted to be jittery and his blood glucose concentration was 1.2 mmol/l (21.6 mg/100 ml). After a supplemental feed the blood glucose concentration was 7.2 mmol/l (130 mg/100 ml), and his symptoms resolved.

On the 15th day of life the result of a random test of blood glucose concentration was 23.5 mmol/l (423 mg/100 ml), and glycosuria was present. During investigation he too was noted to require his wet nappies to be changed at up to hourly intervals.

After five weeks breast feeding was ceased. His weight increased from the 10th to the 70th percentile, and he made normal developmental progress. Although treatment with insulin was considered because of the hyperglycaemia, it was withheld because of his poor social circumstances and his satisfactory growth. Hyperglycaemia (random blood glucose concentrations 11.1–32.1 mmol/l (200–578 mg/100 ml)) and glycosuria persisted until 9 months of age when his blood glucose concentration fell to 6.5 mmol/l (117 mg/100 ml) and the glycosuria resolved. He has remained normoglycaemic and was thriving when last reviewed at the age of 2.

Investigations and results

A glucose tolerance test, including the measurement of plasma insulin concentrations, was performed at the age of 13 weeks in case 1 and 18 days in case 2 (Table). Antibodies against insulin were not detected in serum from case 2 and his mother taken 18 days after birth nor in serum from case 1 when tested at the age of 2 years. Antibodies against

pancreatic islet cells, HEp2 cells, smooth muscle, mitochondria, thyroid microsomes, thyroglobulin, and gastric parietal cells were not demonstrable in the serum of either patient or their mother. Neither patient had a metabolic acidosis, and ketonuria was not present at any time. Case 1 had a normal 0830 hours plasma cortisol concentration of 260 nmol/l (9.2 µg/100 ml) at the age of 13 weeks, and a simultaneous 30 hour collection of urine contained less than 25 nmol of cortisol.

The leucocyte histocompatibility antigen typing for the siblings showed a different inheritance of parental haplotypes for each of the children, case 1 being Aw24, A29; B8, Bw6; DR3, DR5, and case 2 being A3, Aw32; Bw4, Bw6, Bw51, Bw35; DR1, DR6.

Discussion

These brothers had the classic biochemical abnormalities of transient diabetes mellitus of infancy as reported by others—namely, transient hyperglycaemia with glycosuria without either ketonuria or metabolic acidosis being prominent features. However, although transient diabetes mellitus of infancy has been described previously in some infants with a birth weight appropriate for gestational age^{5–10} and in infants not requiring treatment with insulin,^{6 11 12} we could find only one previous report of an asymptomatic infant being diagnosed, and he had been small for gestational age.¹² Thus the infants reported here may either represent part of a broader range of transient diabetes of infancy or have a disorder not previously recognised.

There have been many suggestions as to the aetiology of transient diabetes mellitus of infancy. The possibility of a delay in the functional maturation of the beta cells of the islets of Langerhans with inappropriate insulin secretion has received most support.^{1 2 12} There is evidence in the infants reported here for abnormal insulin secretion and utilisation. The insulin concentrations from case 1 are difficult to interpret fully in the absence of a fasting insulin concentration. The apparent lack of response of the blood glucose concentration with time suggests, however, some form of insulin resistance. The insulin concentration at three hours after challenge is inappropriately low with respect to the blood glucose concentration, suggesting either a sub-optimal response by the beta cells or exhaustion of their insulin supplies.

The inappropriately low concentrations of insulin found for case 2 are similar to those reported by other authors^{2 13} and are consistent with functional immaturity of insulin secretion by the pancreatic

Table *Glucose tolerance tests and plasma insulin concentrations in the two patients*

Time (min)	Case 1		Case 2	
	Blood glucose (mmol/l)	Plasma insulin (mU/l)	Blood glucose (mmol/l)	Plasma insulin (mU/l)
0	19.2	ND	11.9	<4.0
30	ND	ND	11.8	11.0
60	21.1	76	15.0	4.0
90	ND	ND	15.5	7.0
120	20.0	111	16.9	8.0
150	ND	ND	17.1	5.0
180	16.6	32	16.1	4.0

ND=not done

Conversion: SI to traditional units—Glucose: 1 mmol/l≈18 mg/100 ml.

beta cells. The differing responses at the different ages at which these infants were studied may reflect events occurring during the gradual resolution of transient diabetes mellitus of infancy. The results for case 2, studied at 18 days of age, suggest absolute failure of appropriate insulin secretion in the early stages. Those for case 1, who was investigated at age 13 weeks, show a continuing abnormality of glucose disposal in the presence of appropriate insulin concentrations and early exhaustion of insulin secretion. The lack of measurable insulin antibodies suggests that alteration of insulin secretion or function by circulating antibodies is not the cause.

An alternative explanation for the insulin responses is that the glucose concentration at which insulin is caused to be released is inappropriately high in these infants. A threshold for insulin release of 15–16 mmol/l (270–288 mg/100 ml) of glucose in case 1 and 17–18 mmol/l (306–324 mg/100 ml) of glucose in case 2 would explain the observed glucose tolerance results. If this threshold then fell with age a decrease in blood glucose concentrations and resolution of the glycosuria would occur as was seen in the infants reported here.

The occurrence of affected siblings in the families reported by Ferguson *et al*² and ourselves is most consistent with an autosomal recessive mode of inheritance. If the disorder can be asymptomatic, however, it is quite feasible that either parent of an affected neonate may have been affected similarly in infancy without the condition being recognised. This would support autosomal dominant inheritance as does the report of three paternal half siblings (two girls and one boy) with transient diabetes mellitus of infancy reported by Coffey *et al*,^{3,4} each of whom had a different mother.

Reports of a family history of diabetes mellitus in transient diabetes mellitus of infancy have usually been in second or higher degree relatives and often do not distinguish between the genetically distinct insulin dependent and non-insulin dependent diabetes mellitus. The completely disparate HLA typing of the brothers reported here suggests that this form of genetic analysis is unlikely to be of benefit in elucidating the inheritance pattern. Although case 1 inherited the DR3 antigen from his father, case 2 had neither DR3 nor DR4, which are

the two antigens most often associated with insulin dependent diabetes mellitus.¹⁴

It is unclear whether transient diabetes mellitus of infancy has a wide range of clinical presentation, from small for gestational age infants presenting in the neonatal period with dehydration, infection, or failure to thrive to asymptomatic cases such as those reported here, or whether these siblings represent a previously undescribed disorder with abnormal glucose disposal. This question cannot be answered until the pathogenesis of transient diabetes mellitus of infancy has been defined more clearly.

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