Aetiology and genetic basis of neonatal diabetes

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Abstract
A British Paediatric Association Surveillance Unit* study of neonatal diabetes determined a national incidence of 1 in 400 000 live births. Additional cases of transient neonatal diabetes were collected retrospectively. Most cases were of low birthweight at term: none had evidence of an autoimmune aetiopathogenesis. The median requirement for exogenous insulin treatment was three months.

A significant number of cases developed type 2 diabetes in later life. Three of the 11 cases were found to have paternal uniparental isodisomy of chromosome 6. A further patient carried an unbalanced duplication of 6q 22–23, inherited from the father, which localised a potentially imprinted gene for diabetes to this region.

The fact that low birthweight predisposes to type 2 diabetes in later life is well established, but a genetic defect that may relate both to intrauterine growth failure and the development of type 2 diabetes in later life has now been identified.

(Keywords: neonatal diabetes; uniparental isodisomy; chromosome 6; type 2 diabetes.)

Both permanent (PNDM) and transient neonatal diabetes mellitus (TNDM) are extremely rare, with one report estimating an incidence of about 1 in 500 000 live births.1 Typically, the infants are of very low birthweight at term and develop hyperglycaemia, requiring exogenous insulin within the first six postnatal weeks. The condition resolves within three to six months2 but may predispose to diabetes in later life. In 1993 we reported a child born with TNDM but may predispose to diabetes in later life. In 1993 we reported a child born with TNDM who developed diabetes at 13 years of age.3 There was no evidence of islet cell antibody production; HLA typing showed a DR2 haplotype, and for chromosomal and molecular analysis. A number of cases were notified by clinicians to the investigators retrospectively. A clinical history and details of investigations performed at the time of diagnosis was sought and blood requested for genetic analysis for these.

GENETIC INVESTIGATIONS
Molecular DNA was extracted from whole blood using a salt precipitation method.10 All primer sequences were obtained from Genethon or GDB.11 DNA amplification of highly polymorphic microsatellite repeat sequences were also requested to examine islet cell antibody production, insulin and/or 'C' peptide concentrations (a surrogate measure of endogenous insulin production), HLA class II haplotypes, and for chromosomal and molecular analysis. A number of cases were notified by clinicians to the investigators retrospectively. A clinical history and details of investigations performed at the time of diagnosis was sought and blood requested for genetic analysis for these.

Chromosomes were prepared using standard techniques after semi-synchronisation with fluorodeoxy-uridine and release with thymidine.11 A modification of the method of Pinkel et al12 was used for chromosome painting with a whole chromosome paint for chromosome 6 (Cambio).

Results
Three confirmed new cases of neonatal diabetes were reported to the study: two with the 12 month reporting period, giving an incidence rate of about 1 in 400 000 live births. One of these cases died at the age of 3 days with a severe electrolyte imbalance. Eight cases of
classic TNDM and two cases of permanent neonatal diabetes were reported to the investigators retrospectively through the BPASU. A further case of TNDM associated with multiple congenital anomalies was also included.

The characteristics of each patient are given in table 1. Of the 11 TNDM cases, eight had birthweights below the 0.4th percentile for gestational age. There were no consistent dysmorphic features other than two patients with relative macroGLOSSia. Half were not dysmorphic. The median age at presentation was day 3 (range one day to one month). Highest recorded blood sugar concentrations ranged from 13 mmol/l to 74 mmol/l. Insulin or ‘C’ peptide measurement was made at the time of diagnosis for seven cases, and in all, these were undetectable or negligible in the presence of profound hyperGlycaemia. In six cases islet cell antibodies had been assessed at diagnosis all of which were negative. The median duration of exogenous insulin requirement was three months (range one to eight months). Case 10, a boy with transient neonatal diabetes, associated with multiple anomalies, mental retardation, and dysmorphic facies, had convulsions at the age of 7 months with an electroencephalogram (EEG) suggestive of hypsarrhythmia: he subsequently developed deafness, ataxia, and more rarely, renal calcifi. In view of the reported association between neonatal diabetes and X-linked phosphoribosyl-ATP pyrophosphatase (PRPP) synthetase hyperactivity (causing hyperuricaemia, mental and motor retardation, ataxia associated with dysmorphic facies), his PRPP synthetase activity was assessed and found to be normal.

Of the two cases reported with permanent diabetes developing in the neonatal period, one had a birthweight below the 3rd percentile, the other was on the 25th percentile. Both were islet cell antibody negative at diagnosis. ‘C’ peptide concentrations in the one case in which they were measured were within the normal range for that laboratory at 0.5 pmol/l (normal range 0.14-1.39).

Pancreatic material but no antemortem samples were available in the one patient who died. The child was born weighing 1.01 kg. He was initially thought to be around 27 weeks of gestation; however, postmortem examination of the cerebral gyral pattern suggested a gestation of at least 34 weeks. The child had a triangular shaped facies, asymmetrical dilatation of his lateral ventricles, mild hydrophrosis and thrombocytopenia. A screen for congenital infections was negative and the child died of a severe electrolyte imbalance associated with a peak blood sugar concentration of 136 mmol/l. Histological examination of the pancreas revealed normal morphology and numbers of islet cells with normal staining patterns for insulin and no evidence of inflammatory infiltration.

Three of the cases reported to the study with a previous history of TNDM developed diabetes in later life aged 13, 17, and 20 years (cases 5, 6, and 8). In the two cases in which they have been measured, islet cell antibody tests were negative. The case of the girl aged 13 years (case 5) at relapse with type 2 diabetes has been reported before. The boy aged 17 years (case 6) at relapse is 22 years of age at the time of writing, has had intermittent treatment with either sulphonylureas or insulin, and is currently well and off all treatment, which is suggestive of type 2 diabetes. In this case there were reports of hyperGlycaemia in childhood during bouts of infection between the original diagnosis and his final relapse aged 17 years. Similarly, two younger children with previous TNDM aged 3.5 and 9 years (cases 3 and 10) have had periods of intermittent hyperGlycaemia in association with infections. One further case, aged 2 years at the time of writing (case 11), is islet cell antibody negative and currently has normal blood glucose concentrations. However, her ‘C’ peptide concentration at 2019 pmol/l is over three times the normal range for the laboratory (120-600 pmol/l), suggesting that she has insulin resistance.

Using standard cytogenetic techniques, karyotyping seemed normal in eight patients, was not available in four patients, and was abnormal in cases 11 and 13 (table 1) and previously reported by Temple et al. Biparental inheritance of chromosome 6 homologues was shown in nine patients (data not shown) and not tested in one case. Paternal uniparental disomy was found in three cases—cases 5 and 11, as reported before, and case 12 (data not shown).

Discussion

Neonatal diabetes is rare. The incidence established from this study of 1 in 400 000 is close to the figure of 1 in 500 000 suggested by a retrospective study in Germany, and is in keeping with the “1992 diabetes in the under fives study” in which two cases of neonatal diabetes were notified over 12 months. The absence of islet cell antibodies in all cases and the absence of typical type 1 diabetes susceptibility haplotypes in many cases, suggests that the condition is not related to any autoimmune phenomenon. Although it is not possible to define whether the child who died would have had permanent or transient diabetes, the histological findings in this patient are also not those of typical type 1 diabetes. The defect seems to lie in insulin secretion rather than insulin production. Most cases were of low birthweight at term. This could be related to the apparent failure of insulin secretion, as insulin is a known growth factor. Although a number of patients have minor dysmorphic features, severe abnormalities seem to be exceptional. It is interesting to note, however, that macroGLOSSia has been reported in two patients in this study and in other patients with TNDM.

In 1995 we reported the association between TNDM and paternal uniparental isodisomy of chromosome 6 in two unrelated families and suggested a causal relation. Unlike the normal inheritance pattern in which both parents contribute one chromosome of a pair to their offspring, uniparental isodisomy refers to the inheritance of both chromosomes of a pair from one parent only, with no contribution from the other.
In this study we have subsequently identified a further patient (case 12) with TNDM and paternal uniparental disomy of chromosome 6. This phenomenon therefore accounts for 25% of our series of TNDM patients tested. Abramovicz and colleagues\(^1\) also reported paternal uniparental isodisomy 6 in a patient with neonatal diabetes and methylmalonic acidemia, although their patient died aged 16 days and had no identifiable islet cells. The findings of an unbalanced duplication of paternal 6q22-23 in a patient (case 13) with TNDM suggests that the critical area of interest lies within this region. This is supported by one report in which an infant with an unbalanced parental duplication of 6q 23-qter\(^2\) has developed neonatal diabetes. No cases of neonatal diabetes have been reported in association with 18 maternal duplications of this region.\(^3\) In the family of case 13 identical duplications of this region of 6q22-23 have been identified in both the father and paternal grandmother of the proband but neither had TNDM.\(^4\) As the defect is identical in all three this implies an imprinting effect whereby the parental derivation of the abnormality defines its clinical phenotype. If the defect in this condition is solely expressed through the paternal homologue then both paternal uniparental isodisomy of chromosome 6 and paternal duplications in the critical region of chromosome 6 would result in similar effects. We predict that TNDM is due to the overexpression of an imprinted gene at 6q22-23.

Although it is not possible to define the frequency of relapse in children with TNDM, both the findings in this study and others\(^5\) suggest a predisposition to impaired glucose tolerance and type 2 diabetes in later life. This is the first time that a genetic defect has been directly implicated in TNDM. It is interesting to speculate how the findings in this very rare condition might relate to those of Hales et al, who observed an association between low birthweight and subsequent impaired glucose tolerance.\(^6\)

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8 Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at 64. *BMJ* 1991;303:1019-22.


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