Case Report

Neonatal diabetes mellitus

Caroline Stewart, Aileen Redmond

Diabetes mellitus has many forms. Neonatal diabetes mellitus is one of the rarest, with a reported incidence of 1 in 450,000 live births.[1,2] The first case was described by Kitselle (1852) in his own newborn son, who subsequently died.[3] In Northern Ireland, one case might be expected approximately every 16 years; the last documented here was born in 1983.[4] Several literature reviews have highlighted the characteristic clinical picture of this disease.

Neonatal diabetes mellitus is defined as persistent hyperglycaemia within the first six weeks of life, requiring insulin for two or more weeks, in infants of 37 or more weeks gestation.[2,5] Alternative names are temporary idiopathic neonatal hyperglycaemia, neonatal pseudodiabetes mellitus, transient diabetes of early infancy and congenital temporary diabetes mellitus.[5,6] Neonatal diabetes differs from insulin-dependent (type I) diabetes in that it has a highly variable course. Some patients have permanent diabetes, while others have transient or lasting remissions. We report the latest case from Belfast.

CASE REPORT A male infant was admitted to the Royal Belfast Hospital for Sick Children in April 1998, aged six weeks. He was the first child of unrelated parents. His mother suffered from systemic lupus erythematosus and was treated with prednisolone 10 mg daily throughout the pregnancy. She had an uneventful antenatal course, but had proteinuria and mild hypertension at term. She had a normal delivery at 37 weeks of a male infant weighing 2.27 kg (2nd centile). He was well at birth and on account of the maternal history of systemic lupus erythematosus and increased risk of congenital heart block, he had an electrocardiograph before discharge, which was normal.

He fed eagerly and always appeared hungry. His parents contacted the health visitor as he was drinking excessive quantities of formula milk

(3 oz every two hours, equivalent to 265 mls/kg/day). He had no vomiting or diarrhoea, but was not gaining weight. Two days prior to admission, he became very irritable and had some loose motions. His colour became grey and mottled. On admission he was profoundly dehydrated with a depressed fontanelle; his eyes were alert but he was very agitated. He was extremely restless and appeared emaciated, with tachycardia (200/min), tachypnoea (65/min) and fever of 38°C. He showed an unusually high level of consciousness for such a severely dehydrated infant. A ketotic smell was evident. He passed large volumes of dilute urine; urinalysis showed glucose ++++, protein ++, blood + and strongly positive ketones. Blood gas analysis showed marked metabolic acidosis (pH 7.162, pO_2 15.0 kPa, pCO_2 1.41 kPa, HCO_3 3.7 mmol/l and Base excess – 22.7 mmol/l). Biochemical parameters were in keeping with the clinical signs of dehydration and severe hyperglycaemia (serum glucose 73.2 mmol/l, Na 154 mmol/l, K 5.8 mmol/l, Urea 15.1 mmol/l, Creatinine 62 umol/l, Hb 10.7 g/dL, WCC 19.4 x 10^3/ug, platelets 737 x 10^3/ug).

Initial management was with plasma volume expansion with human plasma protein fraction and saline, total volume 40 ml/kg, and intravenous insulin infusion. During rehydration he developed poor peripheral perfusion with oxygen desaturation, opisthotonus and seizure activity. He was transferred to the paediatric intensive care unit and was sedated, mechanically ventilated

---

Royal Belfast Hospital for Sick Children, 180 Falls Road, Belfast BT12 6BE.

E C A Stewart, MRCPCH, DCH, Specialist Registrar in Paediatrics.

A O B Redmond, FRCP(I), FRCPCH, DCH, Consultant Paediatrician.

Correspondence to Dr Stewart.

for three days and treated with anticonvulsants. His blood glucose levels fell slowly with repeated insulin injections. He resumed oral feeds and remained an inpatient for 24 days to establish the insulin and feeding pattern. By the age of 10 weeks his weight had increased to the 25th centile (5.16 kg).

A 14 months his developmental milestones were all normal. He remained on twice-daily subcutaneous medium-acting insulin. Home blood sugars were monitored daily and he had no apparent episodes of hypoglycaemia. HbA$_{1c}$ concentration was 7.1% at age 16 months. To date there has been no evidence of remission and it is probable that diabetes will be a long-term problem.

DISCUSSION

Only 0.5% of children with diabetes develop the disease during the first year of life.[5] The incidence of newly diagnosed type I diabetes mellitus in Northern Ireland is 19.6 per 100,000 children under 15 years, and 18% of cases are under five years at diagnosis.[7] Long term studies of neonatal diabetes world-wide have shown that approximately 42% have permanent diabetes and 58% have a period of remission, with 65% of the transient forms subsequently becoming diabetic again.[2] Infants with the transient form usually become euglycaemic without insulin treatment within the first year.[8]

Babies with neonatal diabetes are usually small for dates term infants, as found in the case presented. In one study, 41 out of 45 babies (91%) had low birth weight (<2nd centile).[2] They develop hyperglycaemia with severe dehydration and minimal ketosis. Seventy-five percent of cases first present with symptoms within 10 days of birth.[5] The picture of a lively, alert but grossly dehydrated child is classical, in contrast to the semicomatose state and glazed-eye appearance usual in severely dehydrated infants.[3, 6] Polyuria is difficult to recognise in the newborn.

With few exceptions, most infants require exogenous insulin. Total daily doses of 0.2-1.0 units/kg are usually sufficient to establish normoglycaemia, and mild hyperglycaemic values are well tolerated. Hypoglycaemia is the greatest complication of insulin therapy, with associated risk of cerebral damage.[3, 6, 9] Small, intermittent doses of regular insulin, along with frequent blood sugar monitoring has been advised to avoid

hypoglycaemia.[10] After initiation of insulin therapy, weight gain usually accelerates.[3, 5]

The frequency of relapse in children with transient neonatal diabetes is difficult to define. One study showed a median duration of exogenous insulin requirement of three months,[1] and another showed a mean insulin requirement of 120 days;[2] and a period of remission until later recurrence of diabetes of 7-20 years (median 13 years).[2] Long term follow-up of the later onset diabetes is not the classical autoimmune related type I form of childhood, but is consistent with type II diabetes with insulin resistance.[1, 8]

Various suggestions as to the pathogenesis of this condition have been proposed, including reduced insulin production from pancreatic dysmaturity,[11] insulin resistance[8, 9] and insulinopenia from a poor response of the pancreatic beta cell to hyperglycaemia.[5] The onset of islet cell damage or destruction is thought to start in utero, as poor insulin secretion by the pancreas has been quantified by low levels of C-peptide in the neonatal period.[4, 12] The fact that most babies are low birth weight may be related to the lack of the anabolic effect of insulin, as insulin is one of the main growth factors in-utero.[1, 12] The autoimmune theory of classical juvenile type I insulin dependent diabetes is not applicable to neonatal diabetes, as there has been no evidence of islet cell antibodies developing.[1, 2, 5] Heredity plays an important role as approximately 25% of neonatal cases have an affected sibling (with type I insulin dependent diabetes), with equal sex ratios.[5, 6] Minorities of patients have shown HLA haplotypes typical for insulin-dependent diabetes (HLA DR3 and DR4).[2]

Recently, the genetic basis of neonatal diabetes has been studied. Shield et al showed on molecular DNA analysis paternal uniparental disomy of chromosome 6 in many cases with the temporary form of neonatal diabetes.[1, 11, 13] This refers to the inheritance of both chromosomes of one pair from one parent only, with no contribution from the other. The findings predict that neonatal diabetes is due to the overexpression of an imprinted gene at 6q22-23,[1, 13, 14] and this gene may prove to be an important factor in the aetiology of more common types of adult diabetes.[14] Hermann et al suggested that the two phenotypes of transient and permanent neonatal diabetes have different genetic backgrounds, as none of the cases with permanent neonatal diabetes

have shown the paternal uniparental disomy of chromosome 6.[15]

Several associations of neonatal diabetes with other developmental or dysmorphic syndromes have been described. Ten cases have been reported of the Wolcott-Rallinson syndrome (a rare autosomal recessive condition characterised by diabetes mellitus in early infancy and multiple epiphyseal dysplasia) all of whom have had permanent diabetes, and a high risk of early mortality from renal impairment.[2, 16] Two cases have been described of brothers with X-linked hyperuricaemia, secondary to phosphoribosyl-ATP pyrophosphatase hyperactivity who became diabetic within the first day of life, both had severe developmental delay.[2] Macroglossia has been reported in patients with transient neonatal diabetes, this feature becomes less pronounced with age.[1, 15]

The combination of systemic lupus erythematosus and pregnancy increases both fetal and maternal risks, with a reported 20-60% flare up of systemic lupus erythematosus, 23% early foetal loss, 50% pre-term delivery and 10% growth retardation.[17] The infants have an increased risk of congenital heart block, neonatal lupus and intra-uterine death. Systemic prednisolone 10 mg/day is well tolerated in planned systemic lupus erythematosus pregnancies.[17] We have found no previous reported cases of maternal systemic lupus erythematosus and neonatal diabetes mellitus, although one infant with initial hypoglycaemia, who was treated with steroids and subsequently developed hyperglycaemia requiring insulin, has been classified as "steroid-provoked" diabetes.[9]

The overall outcome for general health and normal intellectual development is usually good Complications of vasculopathy are rare in long-term follow up-reports over 20 years.[2, 5] The prognosis is worst in permanent diabetes with onset after one month of age, and in association with HLA DR3/DR4 halotypes, and the other rarer associated syndromes.[2]

REFERENCES

1. Shield J P H, Gardner R J, Wadsworth E K J, Whiteford M L, James R S, Robinson D O, Baum J D, Temple I K. Aetiopathology and genetic basis of neonatal diabetes. *Arch Dis Child* 1997; **76**: F39-F42.

2. Von Mühlendahl K E, Herkenhoff H. Long-term course of neonatal diabetes. *N Engl J Med* 1995; **333**: 704-8.

3. Hutchinson J, Keay A J, Kerr M M. Congenital temporary neonatal diabetes. *BMJ* 1962; **2**: 436-40.

4. Halliday H L, Reid M, Hadden D R. C-peptide levels in transient neonatal diabetes. *Diabet Med* 1986; **3**: 80-1.

5. Fosel S. Transient and permanent neonatal diabetes. *Eur J Pediatr* 1995; **154**: 944-8.

6. Lewis S R, Mortimer P E. Idiopathic neonatal hyperglycaemia. *Arch Dis Child* 1964, **39**: 618-24.

7. Patterson C C, Carson D C, Hadden D R. Epidemiology of childhood IDDM in Northern Ireland 1989-1 994: Low incidence in areas with highest population density and most household crowding. *Diabetologica* 1999; **39**: 1063-9.

8. Shield J P H, Baum J D. Transient neonatal diabetes and later onset diabetes: a case of inherited insulin resistance. *Arch Dis Child* 1995; **72**: 56-7.

9. Chance G W, Bower B D. Hypoglycaemia and temporary hyperglycaemia in infants of low birth weight for maturity. *Arch Dis Child* 1966; **41**: 279-85.

10. Mitamura R, Kimura H, Murakami Y, Nagaya K, Makita Y, Okuno A. Ultralente insulin treatment of transient neonatal diabetes mellitus. *J Pediatr* 1996; **128**: 268-70.

11. Milner R D G, Ferguson A W, Naidu S H. Aetiology of transient neonatal diabetes. *Arch Dis Child* 1971; **46**: 724-6.

12. Bappal B, Raghupathy P, de Silvia V, Al Kusaiby S M. Permanent neonatal diabetes mellitus: clinical presentation and epidemiology in Oman. *Arch Dis Child* 1999; **80**: F209-F21 2.

13. Gardner R J, Mungall A J, Dunham I, Barber J C, Shield J P H, Temple I K, Robinson D O. Localisation of a gene for transient neonatal diabetes mellitus to an 18.72 cR3000 (approximately 5.4 Mb) interval on chromosome 6q. *J Med Genet* 1999; **36**: 192-6.

14. Temple I K, Gardner R J, Robinson D O, Kibirige M S, Ferguson A W, Baum J D, Barber J C K, James R S, Shield J P H. Further evidence for an imprinted gene for neonatal diabetes localised to chromosome 6q22-q23. *Hum Mol Genet*, 1996; **5**: 1117-21.

15. Hermann R, Laine A P, Johansson C, Niederland T, Tokarska L, Dziatkowiak H, Ilonen J, Soltesz G. Transient but not permanent neonatal diabetes mellitus is associated with paternal uniparental isodisomy of chromosome 6. *Pediatrics* 2000; **105**: 49-52.

16. Stewart F J, Carson D J, Thomas P S, Humphreys M, Thornton C, Nevin N C. Wolcott-Rallinson syndrome associated with congenital malformations and a mosaic deletion 15q 11-12. *Clin Genet* 1996; **49**: 152-5.

17. Lê Thi Huong D, Wechsler B, Vauthier-Brouzes D, Seebacher J, Letébvre G, Blétry O, Darbois Y, Godeau P, Piette J C. Outcome of planned pregnancies in systemic lupus erythematosus: a prospective study on 62 pregnancies. *Br J Rheum* 1997; **36**: 772-7.