

## Transient Neonatal Diabetes Mellitus

Neonatal diabetes mellitus (NDM) occurs in both a transient (TNDM) and permanent (PNDM) form. Some cases of TNDM occur because of *paternal* uniparental isodisomy (UPD) of chromosome 6. Such UPD has not been demonstrated in PNDM.

Hermann et al studied 6 patients with NDM: 3 with TNDM and 3 with PNDM. Microsatellite markers and human leukocyte antigen alleles were examined using polymerase chain reaction and DNA fragment electrophoresis. Humoral markers of islet cell autoantibodies also were studied. Of the 6 patients with NDM, 1 of the 3 with TNDM and macroglossia carried UPD of chromosome 6. No maternal chromosome 6 sequences were present.

In the 3 patients with PNDM and the other 2 patients with TNDM, no evidence for UPD could be found. None of the 6 had the high-risk type 1 diabetes human leukocyte antigen alleles. Only 1 patient had islet-specific autoantibodies, but did not have glutamic acid decarboxylase antibodies, which are the antibodies most indicative of autoimmune diabetes mellitus. The conclusion by Hermann et al was that patients with transient and permanent forms of NDM have different genetic backgrounds and represent different disease entities. TNDM is often associated with UPD of chromosome 6, suggesting that an imprinted gene on chromosome 6 is responsible for this phenotype. It seems that 2 copies of the paternal allele are necessary for the development of TNDM in the cases with paternal UPD; therefore, it is likely that overexpression of a putative gene located on chromosome 6 alters pancreatic beta-cell maturation and insulin secretion.

The article by Christian et al reports 2 cases of NDM: 1 with PNDM and 1 with TNDM. The latter had macroglossia, which has been reported in some of the 7 previously published cases. These authors suggest macroglossia in the presence of NDM is an unequivocal indicator to search for UDP of chromosome 6.

Hermann R, et al. *Pediatrics* 2000;105(1):49-52.

Christian SL, et al. *J Pediatr* 1999;134(1):42-46.

**Editor's comment:** NDM is a rare disorder, with an estimated incidence of 1 in 400,000 live births. The 3 patients with PNDM had normal biparental inheritance of chromosome 6, and 1 of the 3 with TNDM had demonstrable UPD of chromosome 6. Cases of TNDM without UPD of chromosome 6 may have mutations of a parental gene on chromosome 6, or some other explanation may exist. Genes on chromosome 6 appear to be involved with the development of beta-cell differentiation and/or maturation of the pancreas. Studies for UDP of chromosome 6 should be performed in all cases of NDM.

Fima Lifshitz, MD

**2nd Editor's comment:** Numerous reports now exist distinguishing NDM from other forms of diabetes. Because of the good prognosis, it is suggested that it is worth screening for paternal UPD of chromosome 6 in all cases of NDM. I certainly am in accord with this recommendation.

The mechanism by which insulin is controlled is obviously very complex. Insulin maps to chromosome 11. In the yolk sac, only the paternal insulin gene is expressed in mice. During embryonic development, there is usually biparental expression. However, something on chromosome 6 has to do with control of insulin expression at the time of birth, since UPD can lead to lack of expression from both insulin genes (ie, both the maternal and paternal genes on chromosome 11). Between 6 months and 3 years of age, a different mechanism must control insulin expression, since children outgrow their transient neonatal lack of insulin. This is what happens in patients with TNDM. Normally, in adults there is biparental expression of insulin in the pancreas.

It is of interest that the case with UDP reported by Hermann and colleagues also had macroglossia, which of course occurs in Beckwith-Wiedemann syndrome. Interestingly, in that syndrome there is overgrowth and hyperinsulinemia associated with the macroglossia and paternal UPD for chromosome 11. In the patients with NDM, birth weights are low or low normal.

Judith G. Hall, OC, MD

## Incidence of Diabetes Mellitus and Impaired Glucose Tolerance in Children and Adolescents Receiving Growth Hormone Treatment

Cutfield and colleagues investigated 85 cases of diabetes mellitus, abnormal glucose tolerance, and hyperglycemia reported to the Pharmacia and Upjohn International Growth Study (KIGS) database between 1987 and 1997. The KIGS database is an international pharmacologic survey of the safety and efficacy of GH therapy in children and adolescents. The database includes more than 23,000 children. The information regarding date of diagnosis, presenting symptoms, family history, measurements of antibodies, oral glucose tolerance testing, and risk factors for diabetes was recorded. Data were categorized using the American Diabetes Association (ADA) Expert Committee recommendations for the definition of diabetes. The observed incidence of type 1 diabetes was compared with information available in 12 of the different countries from which the

GH data were extracted. The incidence of type 2 diabetes was matched by age to data from recently reported studies of type 2 diabetes in children from Cincinnati, Ohio, and Japan.

Using the ADA Expert Committee criteria, 42 of the 85 cases reported with abnormal glucose tolerance had to be excluded. Of the 43 remaining cases, 11 were diagnosed with type 1 diabetes, 18 with type 2 diabetes, and 14 with glucose intolerance. Three of the type 1 patients had ketosis, 3 had islet cell antibodies, and 3 had low secretion of C-peptide. In the 18 children who developed type 2 diabetes, 7 had at least 1 risk factor for diabetes. All had persistent diabetes after GH therapy was stopped. The incidence and age at diagnosis of children treated with GH were not different from expected values. However, the