Permanent Neonatal Diabetes

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Neonatal diabetes, i.e., insulin-requiring hyperglycemia, occurring within the first month of life is often associated with intrauterine growth retardation and can be either transient or permanent [1]. Transient neonatal diabetes has been related to abnormalities of chromosome 6, including paternal uniparental disomy and paternal duplication of 6q24, with loss of imprinting [2] and increased risk of diabetes later in life. Mutations in the insulin promoter factor-1, a transcription factor implicated in pancreatic development and regulation of insulin gene expression, lead to permanent neonatal diabetes as a result of pancreatic agenesis [3].

We recently described two infants with intrauterine growth retardation and permanent neonatal diabetes caused by deficiency of the glycolytic enzyme glucokinase [4] and attributed to mutations in the *GCK* gene. We report the clinical data of the two patients and the results of our trial using oral hypoglycemic drugs instead of insulin.

Patient Descriptions

In 1996 we reported on two patients with permanent neonatal diabetes [4,5]. Both were born to consanguineous parents from a large inbred family. One patient was homozygous for a mutation in the donor splice site of exon 8 designated IVS8+2 and the other patient was a compound heterozygous for the IVS8+2 mutation and a mutation in exon 7, namely G264S.

Both patients had been treated with insulin since the diagnosis (a few days of age). Table 1 summarizes the patients' clinical characteristics and genotypes. Patient 1 is currently 10 years old and patient 2 is 20 years old.

The patients were hospitalized for evaluation of their capacity to secrete insulin. After overnight fasting an oral glucose tolerance test was performed: 75 g glucose (25% solution) was given orally for 3 minutes. Patient 1 had undetected C-peptide levels (<165 pmol/L); patient 2 (with compound heterozygosity) had a good C-peptide response, with a rise of fasting C-peptide levels from 412 to 681 pmol/L 30 minutes after glucose ingestion (normal fasting range 334–1,655 pmol/L). In patient 2, insulin treatment was replaced by the hypoglycemic drug repaglinide (Novonorm®, Novonordisk, Denmark), 1 mg before each main meal, and his blood glucose levels (fasting and 2 hours post-prandial) were within the desired range (80–180 mg/dl) without the need for insulin injections.

Comment

The GCK enzyme is a glucose sensor in the beta cell that regulates insulin secretion. GCK deficiency may be regarded as a recessively inherited inborn error of metabolism, with heterozygous carriers having a mild phenotype (MODY2) and homozygotes presenting with permanent neonatal diabetes – a particularly severe phenotype. Our patients, homozygous or compound heterozygous for GCK mutations, shared a similar phenotype with moderate intrauterine growth retardation and severe hyperglycemia that required exogenous insulin therapy shortly after birth. This clinical profile reaffirms the notion that insulin is a potent fetal growth factor and that GCK plays a major role in the regulation of insulin secretion.

We believe that these patients, homozygotes and compound heterozygotes for GCK mutations, may clarify the mechanisms that underlie glucose sensing and insulin secretion by beta cells. We recently demonstrated that homozygosity for the IVS8+2/IVS8+2 mutation is associated with complete loss of GCK activity. The G264S variation seems to be less deleterious, and compound heterozygosity IVS8+2/G264S is associated with some GCK activity accompanied by diminished insulin secretion [4]. We can speculate that in patient 2 the enzymatic activity of GCK has kept beta cells viable, as compared with patient 1 who had no GCK activity. This can explain why patient 2 demonstrated a good response to the

GCK = glucokinase

Table 1. Clinical and genetic characteristics of two patients with neonatal permanent diabetes

Patient	Parents (glucose intolerance)	Birth weight (g)	Birth weight (centile)	Gestational age (weeks)	Age at diagnosis (days)	Blood glucose (mmol/L)	Insulin treatment (units/kg/day)	Glucokinase mutation
1	Both	1,900	<3	40	11	57	1.2	IVS8+2/ IVS8+2
2	Mother	1870	<3	38	2	12	0.9	IVS8+2/G264S

hypoglycemic drug repaglinide, which stimulates insulin secretion by closure of the ATP-sensitive K+ channels (this effect leads to insulin secretion without a need of GCK activity), while patient 1 had no response at all.

References

1. Shield JP. Neonatal diabetes: new insights into etiology and implications. *Horm Res* 2000;53(Suppl.S1):7–11.
2. Stoffers DA, Zinkin NT, StanojevicV, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF-1 gene coding sequence. *Nat Genet* 1997;15:106–10.
3. Njolstad P., Sovik O, Cuesta-Munoz A, Bjokhaug L, Massa O, Barbetti F. Neonatal diabetes mellitus due to complete glucokinase deficiency. *N Engl J Med* 2001;344:1588–92.
4. Njolstad PR, Sagen JV, Bjokhaug L, et al. Permanent neonatal diabetes caused by glucokinase deficiency. *Diabetes* 2003;52:2854–60.
5. Shehadeh N, Gershoni-Baruch R, Mandel H, Nutenko I, Etzioni A. Congenital permanent diabetes: a different type of diabetes? *Acta Paediatr* 1996;85:1415–17.

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