Mutations in the insulin gene can cause neonatal diabetes

September 10 2007

Mutations in the insulin gene can cause permanent neonatal diabetes, an unusual form of diabetes that affects very young children and results in lifelong dependence on insulin injections, report researchers from the University of Chicago and Peninsula University (Exeter, UK) in Sept. 18, 2007, issue of the *Proceedings of the National Academy of Sciences*, published early online.

Although abnormal insulin has been associated with milder cases of type 2 diabetes since the discovery of "insulin Chicago" in 1979, this is the first time that an insulin mutation has been connected to severe diabetes with onset early in life.

The researchers describe 10 mutations, found in 21 patients from 16 families. They suspect that the mutations alter the way insulin folds during its synthesis. They suggest that these improperly folded proteins interfere with other cellular processes in ways that eventually kill the cells that produce insulin.

"This is a novel and potentially treatable cause of diabetes in infants," said study author Louis Philipson, MD, PhD, professor of medicine at the University of Chicago. "It's exciting because each of these patients has one normal insulin gene as well as one mutated gene. If we could detect the disease early enough and somehow silence the abnormal gene, or just protect insulin-producing cells from the damage caused by misfolding, we might be able to preserve or restore the patient's own insulin production."

The effort to learn more about possible genetic causes of neonatal diabetes followed a flurry of publicity last September. Philipson and colleagues at the University of Chicago -- using a protocol developed by co-author Andrew Hattersley, MD, Professor of Molecular Medicine at Peninsula University -- were able to wean a young diabetes patient with a known, treatable mutation in an ion channel protein essential for insulin secretion, off of insulin. This was one of the first such cases in the United States.

Media coverage of that case and outreach by the Juvenile Diabetes Research Foundation stimulated parents of other children diagnosed as infants with type-1 diabetes to contact one of the two centers to request genetic testing. Testing at the University of Chicago uncovered more than a dozen patients with the same treatable mutation.

The publicity also brought calls from the families of more than 70 patients who had been diagnosed with diabetes at less than one year of age but who, as it turned out, did not have a known mutation.

In one family with four affected individuals, tests for known mutations were negative. A combination of linkage studies and candidate-gene testing, however, traced the problem to an abnormal insulin gene. Further tests identified a total of 10 different insulin-gene mutations in patients from 15 other families.

All ten are "missense" mutations; they code for a different amino acid than the one normally found at that position. Such mutations can prevent a protein from folding into its customary shape.

Dysfunctional proteins are usually dismantled by the endoplasmic reticulum, an organelle that can detect misfolded proteins and degrade them. Prolonged demands on this system, however, can cause chronic endoplasmic reticulum stress that can lead eventually to cell death.

The authors postulate that misfolded insulin and its precursors could induce prolonged ER stress, causing the insulin-producing pancreatic beta cells to die.

Treatments aimed at reducing ER stress "might result in better beta cell survival," they suggest. "This could partially ameliorate the diabetic state if secretion resulting from the normal insulin allele could be better preserved."

"Insulin mutations are an important cause of neonatal diabetes," say the authors, accounting for about 20 percent of cases of this rare disorder. Most cases tied to insulin mutation were diagnosed in the first six months of life, with an average age at diagnosis of only 13 weeks. Three of the cases were diagnosed between 6 months and one year after birth.

Neonatal diabetes is considered a genetic disorder by many, said Philipson. Mutations in known genes explain 50 to 60 percent of cases and research teams in the US and Europe are trying to identify a genetic cause of diabetes in the remaining patients.

Even though neonatal diabetes is a rare disease, identification of genes causing it has lead to important knowledge about pancreatic development and function, as well as to more precise diagnosis and improved management of patients.

In 2001, Graeme Bell, PhD, the Louis Block Distinguished Service Professor of Medicine and Human Genetics at the University of Chicago and a co-author of this paper, discovered one of the first gene defects associated with neonatal diabetes, mutation of the gene for glucokinase, an enzyme that helps regulate blood-sugar levels. Bell also discovered several genes that cause other forms of monogenic diabetes and the first gene associated with Type 2 diabetes.

In 1979, co-author Donald Steiner, MD, the A.N. Pritzker Professor in Biochemistry & Molecular Biology and a member of the Howard Hughes Medical Institute at the University of Chicago, was a member of the team that discovered the first mutant insulin, known as "insulin Chicago."

Source: University of Chicago