Neonatal Diabetes Patients Weaned Off Insulin

Patients with certain genetic mutations are being successfully treated with oral sulfonylureas instead.

BY CHRISTINE KILGORE
Contributing Writer

When Dr. Fran Cogen, diabetes program director at Children's National Medical Center in Washington, read last year that patients with neonatal diabetes caused by particular genetic mutations could be successfully switched from insulin therapy to oral sulfonylureas, her mind raced.

"We realized we probably had several children with diabetes who were diagnosed under a year of age," she said. The news about the mutations and treatment "was very interesting to me."

She called Dr. Louis Philipson, the endocrinologist at the University of Chicago who—according to the article—had just treated a 6-year-old girl found to have a mutation in the KCNJ11 gene with high-dose sulfonylurea therapy, weaning her off her insulin pump.

After hearing about the treatment firsthand, she called one of the patients at Children's, an 18-year-old male whose diabetes had been diagnosed when he was a young infant. Genetic testing revealed that he too had the KCNJ11 mutation, and the family is now gearing up for treatment and a future that, at least in the short term, may well not involve insulin therapy.

Researchers who have spent the last several years trying to demonstrate that diabetes diagnosed before 6 months of age is almost never autoimmune hope that recent developments and reports in the literature will prompt more endocrinologists to take note of their patients' histories and order genetic tests when appropriate.

Neonatal diabetes, which is estimated to occur in 1 of every 100,000 newborns, is one of several clinical presentations in children for which a diagnosis of monogenic diabetes should be considered, experts say. A variety of genetic causes has been identified, but experts now believe that between 30% and 50% of children diagnosed with diabetes under 6 months of age have one of two mutations that affect the ATP-sensitive potassium channel of the beta cell.

The most common cause of permanent neonatal diabetes mellitus—the type of neonatal diabetes that has required continual insulin treatment from diagnosis onward—is a mutation in the KCNJ11 gene, which encodes a subunit of this channel called Kir6.2.

The mutation makes Kir6.2 less sensitive to the build-up of ATP and the channel thus fails to close in the presence of glucose (and increased intracellular ATP), leading to drastic reductions in insulin secretion.

Another less common cause is associated with mutations in the ABCC8 gene, which encodes the sulfonylurea receptor (SUR1)—another subunit of the beta cell's ATP-sensitive potassium channel.

Research on the mutations—and the notion that sulfonylureas can close this channel through an ATP-independent route—culminated last August when Dr. Andrew Hattersley of Peninsula Medical School in Exeter, England, and colleagues from several countries reported in the New England Journal of Medicine that 44 of 49 (90%) patients with kir6.2 mutations—aged 2 months to 36 years—successfully discontinued insulin after receiving high doses of sulfonylureas.

Glycosylated hemoglobin levels improved in all the patients, from a mean of 8.1% before sulfonylurea treatment to 6.4% at 12 weeks after cessation of insulin.

At 1 year, as the patients continued with much lower doses of sulfonylureas, the improved glycemic control was sustained—without any reports of severe hypoglycemia or any significant change in the frequency of hypoglycemia episodes (N. Engl. J. Med. 2006;355:467-77). As of last month, the patients' responses have been maintained past 2 years, Dr. Hattersley said in an interview.

Investigators of a second study published in the same issue of the journal reported that five out of nine patients with the ABCC8 mutation were also successfully switched from insulin therapy to oral sulfonylurea therapy (N. Engl. J. Med. 2006;355:456-65).

The long-term outlook for these patients, however, is uncertain. "We don't know, will they start having hypoglycemia? Will they start having inappropriate weight gain? Does the effectiveness (of sulfonylureas) wear out?" said Dr. Jay Cohen, medical director of the Endocrine Clinic in Memphis, Tenn.

'It's intriguing to me to wonder, what happens 10 years from now? Will these children be different from those who burn out their pancreas?'

Formation of a registry to assess long-term safety and efficacy would be helpful, he said, since "it's likely that no one institution will have more than one or two or three kids [with neonatal diabetes]."

Dr. Naomi Neufeld, professor of pediatrics at the University of California, Los Angeles, said she agrees that all children with neonatal diabetes should now be screened for the mutations, but she said she would approach treatment with some words of caution.

"It's intriguing to me to wonder, what happens 10 years from now? Will these children be different from those who burn out their pancreas?" she said.

Dr. Philipson said that while no one knows for sure, he suspects that they will indeed be different. "We know in type 2 diabetes, there's a significant failure of sulfonylureas over time. But these are [often] patients who are obese, insulin resistant, maybe hyperlipidemic, or [who] have other aspects of the metabolic syndrome that could impact negatively on their beta-cell function," he said in an interview.

"These kids [with neonatal diabetes] are thin. All the children that I've seen and that Dr. Hattersley's seen have normal or below-normal [body mass indexes]. They're highly sensitive to insulin, and the insulin secretion we're looking for is modest," he said.

In addition to Lilly Jaffe, the little girl he treated last summer, Dr. Philipson and his colleague Dr. Graeme Bell have treated six other children from across the country. He estimates about 20 children have been treated in the United States. "And there are at least several hundred others … who could be reached," he said.

Tests for the mutations are commercially available through at least one company, Athena Diagnostics, he said.

Dr. Philipson has used glyburide, the sulfonylurea used in most of the patients in Dr. Hattersley's study, in an inpatient protocol that allows rapid switching from insulin. His protocol resembled that followed by investigators in Dr. Hattersley's study, which entailed starting glyburide at a dosage of 0.1 mg/kg twice daily and increasing the dosage by 0.2 mg/kg per day. In an outpatient protocol that some of the investigators chose, glyburide was introduced at 0.1 mg/kg per day and increased by that amount once a week.

In Dr. Hattersley's study, the median dosage of glyburide that was required for insulin independence was 0.45 mg/kg per day.

Lilly Jaffe is now receiving much smaller doses of glyburide twice a day, and "remarkably, her morning blood sugars are still quite reasonable," said Dr. Philipson.

In Washington, Dr. Cogen said she will be "less worried" about using high doses of glyburide in her 18-year-old patient than she would be in a younger child, though she plans to get the word out to all of her patients with neonatal diabetes. "To be able to take a patient off of insulin is so exciting—it's everybody's dream." ■

Some Normal-Weight Teens May Be at Risk for Insulin Resistance

BY PATRICE WENDLING
Chicago Bureau

TUCSON, ARIZ. — There are 1.2 million previously unidentified normal-weight adolescents nationally who may be at increased risk of insulin resistance, Dr. Ann Rodden, said at the annual meeting of the North American Primary Care Research Group.

Adolescents with a body mass index (BMI) in the 75th-84.9th percentile and those who have low levels of physical activity were at increased risk for insulin resistance, according to data obtained in a secondary analysis of the National Health and Nutrition Examination Survey (NHANES) during 1999-2002.

Prevalence estimates suggest that more than 8.5 million American adolescents have insulin resistance. Of these, more than 1.2 million are in the 75th-84.9th BMI percentile. The American Diabetes Association considers adolescents with a BMI at or above the 85th percentile to be at risk for insulin resistance, said Dr. Rodden, department of family medicine, Medical University of South Carolina, Charleston.

"There is a population of adolescents that right now we do not consider to be at risk of insulin resistance and that we should be looking at in addition to those already identified," she said.

The analysis was based on a nationally representative sample of 1,806 nondiabetic, nonpregnant adolescents aged 12-19 years who were participating in the NHANES study. Insulin resistance was calculated using the Homeostasis Model Assessment (HOMA) method, with a value of more than 3.16 used as the cutoff for insulin resistance.

Of these, 581 adolescents had insulin resistance, representing 30,855,840 adolescents in the U.S. population. Their mean age was 15 years. Overall, 28% of all females and 27% of all males who were evaluated had insulin resistance. Among individual ethnic groups, whites were less likely to have insulin resistance (28.2%) than were blacks (34.9%) or Hispanics (34.5%). Among those who reported physical activity levels of less than an hour a week of heavy activity, 38% had insulin resistance.

Only 9.2% of those in the under-50th BMI percentile and 13.3% in the 50th-74.9th percentile had insulin resistance. Of note was that about one-third (33.8%) of normal-weight adolescents in the 75th-84.9th BMI percentile had insulin resistance, as did 37.8% in the 85th- 94.9th percentile and 72.8% in the 95th or higher BMI percentile, Dr Rodden reported.

With a logistic regression analysis adjusting for age, ethnicity, gender, poverty income ratio, and carbohydrate intake, the odds of developing insulin resistance were four times higher for adolescents in the 75th-84.9th percentile (odds ratio 4.28) and the 85th-94.9th percentile (OR 4.30), and nearly 18 times higher for overweight adolescents in the 95th or higher percentile (OR 17.91). The risk was not significantly increased for adolescents in the two lowest BMI percentiles.

Being less active was also significantly associated with increased risk of insulin resistance, particularly among those with less than an hour a week of heavy activity (OR 4.38). But cardiovascular fitness level was not. This finding suggests that physical activity may have metabolic benefits irrespective of the level of fitness achieved, Dr. Rodden said.

The study was limited by the lack of a universally accepted definition for insulin resistance in adolescents, and self-reported physical activity data. ■

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