Diabetes in Neonates Usually Is Not Type 1

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FROM A CONFERENCE ON MANAGEMENT OF DIABETES IN YOUTH

KEYSTONE, COLO. — The last half-decade has brought the startling insight that fewer than 1% of cases of diabetes diagnosed before 6 months of age are type 1 diabetes, the diagnosis traditionally given.

Moreover, 30%-70% of cases of diabetes in infants younger than age 6 months are caused by a defect in insulin signaling that's correctable with oral sulfonylurea therapy, a far superior option than insulin therapy, Dr. Georgeanna J. Klingensmith said at the meeting, sponsored by the Children's Diabetes Foundation at Denver.

"If you can use oral sulfonylurea therapy for these, the treatment is actually better—you get better glycemic control—and it's obviously a lot easier on the family not to have to give multiple injection therapy," observed Dr. Klingensmith, chief of the pediatric clinic at the Barbara Davis Center for Childhood Diabetes and professor of pediatrics at the University of Colorado at Denver.

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DR. KLINGENSMITH

For this reason, genetic testing for neonatal diabetes mellitus (NDM), as the condition is called, should be ordered promptly in any infant who develops diabetes before age 6 months. The testing is also being ordered for adolescents and adults on insulin therapy whose disease began before age 6 months.

The genetic defects most responsive to oral sulfonylurea therapy involve the KCNJ11 gene, responsible for the Kir6.2 protein in the potassium channel of pancreatic beta cells, and the SUR1 gene, involved in the potassium channel's sulfonylurea receptor. These genetic defects prevent the potassium channel from closing appropriately. Oral sulfonylurea therapy overrides these defects and restores normal potassium channel function.

Only low-dose oral sulfonylurea therapy is required when NDM is diagnosed in a child. The recommendation in the International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines on monogenic diabetes is to start at one-quarter of the normal adult dose, said Dr. Klingensmith, an editor of the guidelines, available at www.ispad.org.

Adults with NDM who've been on insulin for years typically require very large doses of oral sulfonylurea drugs, at least initially, although in Dr. Klingensmith's experience the doses required diminish over time. This is consistent with animal models of NDM, which suggest that over time the genetic defects result in depletion of insulin granules. The clinical experience with adults suggests that high-dose sulfonylurea therapy may allow replenishment of these insulin granules, she said.

"There's no apparent harm from patients with NDM going unrecognized and being treated with insulin for years or decades before switching to oral sulfonylureas," according to the endocrinologist. "I have two patients who were on insulin for 16 and more than 20 years before we knew about NDM and are now doing well on oral sulfonylureas."

The pathophysiology of NDM most commonly involves a defect in the Kir6.2 protein such that adenosine triphosphate can't bind to the potassium channel and cause it to close in response to rising glucose levels within the pancreatic beta cell. If the potassium channel can't close, the cell membrane won't depolarize, an act necessary in order for the calcium channel to open. An open calcium channel is prerequisite to the influx of intracellular calcium that causes insulin granules to rise to the cell surface, with resultant insulin secretion.

"The problem in NDM is not that they can't make insulin, but that they can't recognize that they need to make

insulin because they don't have any closure of the potassium channel," Dr. Klingensmith explained.

Like patients with type 1 diabetes, infants with NDM can and often do present in diabetic ketoacidosis. They do not have pancreatic islet or other autoantibodies, but they are vulnerable to hypoglycemia.

"These babies can get hypoglycemia secondary to oral sulfonylureas. I think the parents and eventually the child need to understand that they do have diabetes. They have severe diabetes, so they need their medication regularly and they need to do blood testing because they can become hypoglycemic," she stressed.

Although the genetic testing can be done by commercial laboratories, Dr. Klingensmith suggested physicians consider the free testing available from Peninsula Medical School in Exeter, England, where the discovery of the importance of the KCNJ11 gene was made.

With the help of grant support provided by the ISPAD, the Exeter group will test for free anyone diagnosed with diabetes before age 6 months, even if they're now in middle age.

The Exeter group also tests for other genetic causes of NDM in addition to KCNJ11 and SUR1 defects, including defects in the MODY2 gene as well as Wolcott-Rallison syndrome. The Exeter group's Web site (www.diabetesgenes.org) contains downloadable consent forms and detailed instructions on the blood samples they need. The investigators require blood from the child and both parents, or alternatively the child, one parent, and an unaffected sibling, so they can more readily determine whether any novel mutations they find are functional.

Dr. Klingensmith reported no financial conflicts. ■