

MODY Seen in 5% of Antibody-Negative Children

BY MIRIAM E. TUCKER
Senior Writer

CHICAGO — Approximately 5% of antibody-negative/C-peptide-positive children and adolescents diagnosed with diabetes in the United States may have Maturity-Onset Diabetes of the Young rather than type 2 diabetes, Dr. Lisa Gilliam reported at the annual scientific sessions of the American Diabetes Association.

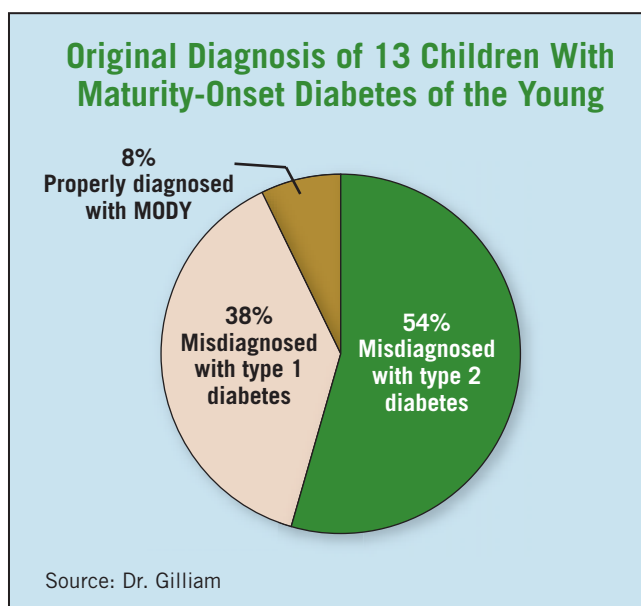
Maturity-Onset Diabetes of the Young (MODY), first described in the mid-1970s, is a clinically heterogeneous group of disorders characterized by nonketotic diabetes, an autosomal dominant pattern of inheritance, and typical onset below the age of 25 years. It can arise from mutations in any one of at least six different genes associated with beta-cell function. The most common form, MODY3, arises from a mutation in the HNF (hepatocyte nuclear factor)-1[α] gene (N. Engl. J. Med. 2001;345:971-80).

New findings suggest that MODY is underrecognized and often inappropriately treated. “Clinicians need to maintain a high level of suspicion for MODY in antibody-negative children who have residual beta-cell function, and certainly consider screening in individuals who meet the

classic criteria for MODY,” said Dr. Gilliam, of the division of metabolism, endocrinology and nutrition at the University of Washington, Seattle, in an interview.

The data come from SEARCH, a federally funded study of physician-diagnosed diabetes in individuals under 20 years of age in six U.S. centers located in Southern California, Colorado, Ohio, Washington state, and South Carolina. The coordinating center is in Winston-Salem, N. C. (www.searchfordiabetes.org).

Of 3,993 participants in whom diabetes-associated autoantibodies and fasting C-peptide were measured, 438 were autoantibody-negative. Direct sequencing for the HNF-1[α] gene was performed in a subset of 266 patients who were autoantibody-negative and who had fasting C-peptide levels greater than 0.8



ng/mL. Among those, 13 patients had 14 gene mutations, including 7 that had not previously been described.

Only 1 of the 13 patients had been clinically diagnosed with MODY, while 5 had been misdiagnosed with type 1 diabetes and 7 with type 2 diabetes. Seven were currently being treated with insulin, and none were taking sulfonylureas, which is the recommended pharmacologic treatment for MODY3. MODY patients are “exquisitely sensitive” to sulfonylureas, which are cheaper and easier to take than multiple daily insulin injections, Dr. Gilliam explained.

Several clinical characteristics helped distinguish MODY3 from type 1 diabetes. Compared with those 3,484 individuals with type 1 diabetes in this study, the 13 MODY3 patients were less likely to have had weight loss (46% vs. 74%) or polyuria (54% vs. 93%) at diagnosis. The MODY group also tended to be older, heavier (body mass index z score 1.5 vs. 0.6), much more likely to have

a parent with diabetes (62% vs. 14%), and much less likely to have medium- to high-risk HLA types (46% vs. 85%). Just 3 of the 13 were non-Hispanic white (23%), compared with 69% of the type 1 group.

In contrast, virtually no clinical or biochemical characteristic was identified that could help in distinguishing MODY3 from type 2 diabetes on an individual basis. Although the MODY group was somewhat younger and less obese than the type 2 patients, there was a great deal of overlap between the two groups. The type 2 patients were just as likely as the MODY group to have a positive family history for diabetes—including an autosomal dominant three-generation family history—and fasting C-peptide levels were similar, Dr. Gilliam said.

“With the prevalence of obesity and type 2 diabetes increasing in the pediatric population, it’s becoming more challenging to distinguish MODY from type 2 diabetes,” she noted.

Because genetic screening is very expensive, at this point it’s not feasible to recommend it in every antibody-negative child or adolescent with residual fasting C-peptide. “However, particularly as costs come down for this type of screening, I predict that the screening cost will be outweighed by the benefit to the subset of patients who would be diagnosed appropriately with MODY,” she said in the interview.

Specifically, that benefit would include lower cost, less hassle, and greater treatment efficacy for patients who could be switched from insulin to a sulfonylurea, she noted.

Genetic testing for MODY is available at 11 clinical laboratories around the world, including 2 in the United States. Such facilities can be found by searching with the keyword “MODY” at www.genetests.org. ■



Inhaled Insulin Appears Safe for Children, Three Studies Show

SAN FRANCISCO — Although inhaled human insulin has been approved by the FDA for use only in adults, it appears to be safe for use in children with type 1 diabetes, according to a poster presentation by Dr. Richard C. Ahrens at the international conference of the American Thoracic Society.

Combining the results of three studies comparing human insulin inhalation powder (Exubera) to subcutaneous insulin in 301 children aged 6-17 years, Dr. Ahrens, of the University of Iowa, and his colleagues concluded that the pulmonary safety profile of inhaled insulin in children is similar to that previously reported for adults.

The study was sponsored by Pfizer Inc., which manufactures Exubera. Two of the three investigators were Pfizer employees.

The children were initially followed for 24 weeks in the case of two of the trials, and for 12 weeks in the other trial. At the studies’ conclusion, the children had the option of entering a long-term uncontrolled extension study in which all patients received inhaled insulin.

As in adults, the children using inhaled in-

sulin showed small but consistent decreases in forced expiratory volume in 1 second (FEV₁) and in diffusion capacity of the lung for carbon monoxide (DL_{CO}). These decreases were evident at 12 and 24 weeks.

However, when the mean change from baseline in FEV₁ was expressed as a percentage of that predicted, there were no significant changes over time, indicating that the children had normal lung growth while receiving inhaled-insulin therapy.

According to the investigators, pulmonary adverse events among the children were generally consistent with those seen in adults. Among the children taking inhaled insulin, 31.4% experienced cough, compared with 9.5% of the children taking subcutaneous insulin. The incidence of dyspnea was 3.3% among the children taking inhaled insulin and 0% among the children taking subcutaneous insulin.

The only serious adverse event was a case of pleural effusion, which occurred in one of the children taking inhaled insulin during the uncontrolled extension phase.

—Robert Finn