Maturity-Onset Diabetes of the Young Seen in 5% of Antibody-Negative Children with Diabetes

Approximately 5% of antibody-negative / C-peptide–positive children and adolescents diagnosed with diabetes in the USA may have Maturity-Onset Diabetes of the Young (MODY) rather than type 2 diabetes, Dr. Lisa Gilliam reported at the ADA.

MODY, first described in the mid-1970s, is a clinically heterogeneous group of disorders characterised by non ketogenic 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[alpha] gene (N Engl J Med. 2001; 345: 971-80).

New findings suggest that MODY is under recognised 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.

The data come from SEARCH, a federally funded study of physician-diagnosed diabetes in individuals under 20 years of age in six U.S. centres located in Southern California, Colorado, Ohio, Washington state, and South Carolina (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[alpha] 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 sulphonylureas, which is the recommended pharmacologic treatment for MODY3. Not only are MODY patients “exquisitely sensitive” to sulphonylureas, but they also are cheaper and easier to take than multiple daily insulin injections.

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, 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.

With the prevalence of obesity and type 2 diabetes increasing in the paediatric population, it will become more challenging to distinguish MODY from type 2 diabetes.

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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, the screening cost will be outweighed by the benefit to the subset of patients who would be diagnosed appropriately with MODY. Specifically, that benefit would include lower cost, less hassle, and greater treatment efficacy for patients who could be switched from insulin to a sulphonylurea.

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

**New Guidelines Target Management and Prevention of Hyperglycaemic Crises in Adults With Diabetes**

The ADA has issued a consensus statement addressing the diagnosis, treatment, and prevention of DKA and hyperosmolar hyperglycaemic state (HHS) are the two most serious acute metabolic complications of diabetes. Mortality in patients with DKA is less than 5% in experienced centres, whereas the death rate in HHS remains high, at about 11%. The annual incidence rate for DKA ranges from 4.6 to 8 episodes per 1,000 patients with diabetes, reported Dr. Abbas E. Kitabchi and his associates (Diabetes Care 2006;29:2739-48 - http://care.diabetesjournals.org).

Although most patients with DKA have autoimmune type 1 diabetes, patients with type 2 diabetes (T2DM) are also at risk during acute stress, such as trauma, surgery, or infection. During the past decade, an increasing number of DKA without precipitating causes have been reported in T2DM.

Inadequate or inappropriate insulin therapy and infection are the two most common precipitating factors in both DKA and HHS. Whereas HHS typically evolves over several days to weeks, the evolution of DKA in type 1 or T2DM tends to be much shorter.

The classic picture of DKA includes a history of polyuria, polydipsia, weight loss, vomiting, abdominal pain, dehydration, weakness, mental status change, and coma. With HHS, the most common clinical presentation is altered sensorium, along with signs of dehydration.

Initial laboratory evaluations of DKA or HHS should include plasma glucose; U & E, creatinine with calculated anion gap; serum ketones; osmolality; urinalysis and urine ketones; arterial blood gases; and FBC. If clinically indicated, an ECG, chest x-ray; and urine & sputum MCS, or blood cultures. Patients with low-normal or low serum potassium have severe total-body potassium deficiency and require cardiac monitoring and vigorous potassium replacement, because treatment lowers potassium further and can provoke cardiac dysrhythmia.

Treatment of DKA and HHS requires the correction of dehydration, hyperglycaemia, and electrolyte imbalances, as well as the identification of precipitating events.

Fluid therapy is directed toward expansion of the intravascular and extravascular volume and restoration of renal perfusion. Adequate rehydration with subsequent correction of the hyperosmolar state has been shown to result in a more robust response to low-dose insulin therapy.

Unless the episode of DKA is uncomplicated and mild or moderate, regular insulin by continuous intravenous infusion is the treatment of choice. However, recent data suggest that the use of subcutaneous rapid-acting insulin analogues in the management of patients with uncomplicated DKA could allow for treatment in general wards or emergency departments, thus avoiding admission to the intensive care unit. Direct measurement of beta-hydroxybutyrate in the blood is the preferred method for monitoring DKA, and has become more convenient with the recent development of bedside meters capable of measuring beta-in whole blood.

Criteria for resolution of DKA include glucose less than 11.1 mmol/l, serum bicarbonate greater than or equal to 18 mEq/L, and venous pH greater than 7.3. When the patient is able to eat, a multiple-dose schedule involving a combination of basal and prremeal bolus insulins should be initiated as needed to control plasma glucose. To prevent hypokalaemia, potassium replacement is initiated after serum levels decrease to less than 5.3 mEq/L, assuming the presence of adequate urine output at 50 mL/hour.

The use of bicarbonate in DKA remains controversial. At a pH greater than 7.0, the administration of insulin blocks lipolysis and resolves ketoacidosis without any added bicarbonate. However, limited data do support the use of bicarbonate – along with potassium supplementation – in patients with pH values lower than 7.0, and particularly in those with levels lower than 6.9, for whom the risk for severe acidosis is elevated.

Routine use of phosphate is not indicated in the treatment of DKA or HHS; data suggest it provides no clinical benefit. However, careful phosphate replacement may be indicated in some patients with cardiac dysfunction, anaemia, or respiratory depression in order to minimise the risks associated with hypophosphataemia.

Many cases of DKA and HHS are preventable by better education, access to medical care, and effective communication. Sick-day management should be reviewed periodically with all diabetic patients. They should be advised never to discontinue insulin, and to seek professional advice at the onset of illness. Particular attention should be paid to the prevention of dehydration, especially in elderly patients.
10-year follow-up study has cast doubt on the value of population screening for type 2 diabetes, after finding no differences in health outcomes between people with diabetes identified on screening and people with diabetes who were not screened.

Specialists from centres in London and Cambridge, UK, studied data from the Ely Study, involving screening by oral glucose tolerance test (OGTT) at a single general practice in the city of Ely.

In 1990, one-third of registered patients aged 40-64 years without known diabetes were selected at random to be offered 5-yearly screening by OGTT (the screened group). A further one-third were randomly selected for OGTT testing plus outcome measurement 10 years later (the unscreened group).

About three-quarters of the patients with diabetes in each group attended for the 10-year assessment (99 in the screened group, with diabetes mainly screen-detected; 67 in the unscreened group, with diabetes mainly diagnosed clinically). The patients in the screened group were significantly older than those in the unscreened group (mean 68.4 years versus 66.1 years, respectively), but there were no significant differences in duration of diabetes (mean 6.2 years versus 5.1 years, respectively).

The 10-year assessment revealed no significant differences between the two groups in any of the parameters measured: body mass index, HbA1c, systolic blood pressure, diastolic blood pressure, microalbuminuria, neuropathy, retinopathy, ischaemic heart disease, and scores for physical function, general health and mental health on the SF-36 questionnaire.

The researchers concluded that the differences in outcomes between the two groups "were small 10 years after commencement of screening." They added: "This study cannot exclude the possibility that early detection may reduce the long-term risk of complications, but stronger evidence of net benefit is needed before population screening can be recommended."

Insulin Resistance Thought to Play Role in Both LADA and Type 2 Diabetes

Insulin resistance may play a role in the pathogenesis of latent autoimmune diabetes in adults (LADA), reported Sofia Carlsson et al of Karolinska Institutet, Stockholm, in the January issue of Diabetologia. In their population-based study, they found that increased age, BMI of 30 kg/m² or higher, and physical inactivity were equally significant risk factors for type 2 diabetes and for LADA. "The association that we see between these factors and LADA suggests a role for insulin resistance in the development of LADA," they wrote (Diabetologia 2007;50:55-8).

They looked at incident cases of diabetes identified in two surveys conducted as part of the Nord-Trøndelag Health Study, a prospective, population-based study open to all residents, aged 20 years+, of the Norwegian county of Nord-Trøndelag. Similar surveys were conducted from 1984 to 1986 (baseline) and from 1995 to 1997 (follow-up). The surveys included a clinical examination and questionnaires on health and lifestyle factors.

The first survey enrolled 76,885 subjects, or 90% of the eligible population, and the second survey enrolled 65,258 subjects, or 71% of the eligible population. Data were available for a cohort of 38,800 men and women who participated in both surveys and were initially free of diabetes.

Patients who reported diabetes only in the follow-up survey were asked to visit the clinic, where they underwent measurements of fasting blood glucose, fasting C-peptide, and antibodies against glutamic acid decarboxylase (GAD). Anti-GAD antibody results were expressed as an index value relative to a standard serum, with a value greater than 0.08 defined as positive.

Patients who were treated with insulin within 6 months of diagnosis and who were either anti-GAD positive or who had fasting C-peptide levels less than 150 pmol/L, were classified as having type 1 diabetes. Patients who were anti-GAD positive and who had not been treated with insulin within 12 months of diagnosis were classified as having LADA. Patients who were anti-GAD negative and had not been treated with insulin within 12 months of diagnosis were classified as having type 2 diabetes.

During the 11-year period between the first and second surveys, 18 patients developed type 1 diabetes, 81 patients developed LADA, and 738 patients developed type 2 diabetes. The risk of developing LADA or type 2 diabetes, but not type 1 diabetes, increased progressively with age. The relative risks of developing diabetes for subjects aged 60 or older, compared with subjects in the 18-39 year age group, were 6.78 for type 2 diabetes and 5.62 for LADA. In addition, physical inactivity was associated with development of type 2 diabetes and LADA.

A BMI of 30 kg/m² or higher was associated with significantly increased risks of LADA (relative risk 15.37) and type 2 diabetes (relative risk 15.0), but not of type 1 diabetes (relative risk 1.16). "In our population, 70% of the cases of LADA could be attributed to overweight," wrote the authors. "If these results are confirmed in other populations, they imply that we can expect increasing rates of LADA to result from the current obesity epidemic and demographic transition."
significant percentage of diabetes in children in all age groups is probably non-autoimmune in origin, with a remarkable increase after age 10 years, Jian Wang et al reported. This conclusion was drawn from a study in which 859 children with new diabetes were tested for four anti-islet autoantibodies: insulin autoantibodies (IAA), glutamic acid autoantibodies (GAA), islet cell autoantibodies (ICA), and islet cell autoantibody 512 autoantibodies (ICA512AA), and including two constructs of ICA512 (ICA512bdc and ICA-2ic). HLA genotypes, BMI, and HbA1c levels were also measured. The study included 441 males and 418 females, ranging in age from 1 month to 18 years (mean 10.7 years). Overall, 54% were diagnosed between ages 9 and 14 years (J. Clin. Endocrinol. Metab. 2007;92:89-92).

With the three autoantibody assays of micro-IAA, GAA, and ICA512AA (ICA512bdc construct only), the positivity of autoantibodies was 79.4% (689 of 868). But by using the alternative ICA512 construct, IA-2ic, in 177 patients, followed by ICA testing in 167 patients, it was possible to identify 18 additional autoantibody-positive patients, yielding a final rate of 81.5% for autoantibody-positivity.

This finding meant that a surprising 18.5% were autoantibody negative. Previously, it was reported that about 4%-7% of patients with newly diagnosed type 1 diabetes are autoantibody negative, according to Wang et al. Autoantibody negativity was equally distributed in both genders. Autoantibody positivity was 83% among children with diabetes onset under the age of 4 years, and the rate declined rapidly with age, reaching about 20% after age 15 years. Autoantibody negativity varied significantly by ethnic group. Autoantibody negativity was identified in 15% whites, 29% Hispanics, and 38% blacks. The difference between Hispanics and blacks in autoantibody negativity was not significant, and the difference among all three races was mostly in children older than 14 years. Autoantibody negativity was significantly increased in children within three BMI cut-offs: 27.5% for BMI > 1 standard deviation above the mean, 36.6% for BMI > 1.5 standard deviations above the mean, and 43.4% for BMI > 2 standard deviations above the mean. Hispanic and blacks aged 10+ with higher BMIs than those of whites had significantly increased autoantibody negativity. The data are consistent with previous observations that Hispanic and black children have a greater tendency to develop type 2 diabetes.

There was no significant difference in HbA1c levels between the autoantibody +ve and –ve patients, although HbA1c levels were positively correlated with age of diabetes onset in both groups.

“A reciprocal prevalence of autoantibodies associated with ages suggests a potential mechanism of differential islet autoimmune pathogenesis at different age groups,” the authors concluded.

Phosphodiesterase type-5 inhibitors should be considered a primary treatment for ED in men with diabetes mellitus, according to a meta-analysis of the Cochrane Database of Systematic Reviews. It called the drugs safe and effective, stating that “their relative as well as absolute effect on sexual activity is clinically favourable, with consistent statistical significance." The analysis revealed that their effect may wane at low doses in those with uncontrolled diabetes, and higher doses may be required for this particular subgroup (Cochrane Database Syst. Rev. 2007 Jan 24. Erectile dysfunction (ED) is a common complication of diabetes, with about half of the men experiencing ED at least once in the course of their disease. Different strategies have been tried to overcome this complication prior to PDE-5 inhibitors, but none proved definitive.

Eight randomised controlled trials in which 976 men received a PDE-5 inhibitor and 741 received placebo for the treatment of ED were analysed. Overall, 80% of the participants had type 2 diabetes. Six trials compared sildenafil with placebo at doses between 25 mg and 100 mg. The other two trials compared tadalafil 10 mg and 20 mg with placebo, and vardenafil 10 mg and 20 mg with placebo. Patients used the medication no more than once daily for 10 days in one study, 16 weeks in one study, and 12 weeks in the remaining trials. Five of 8 trials included scores for Index of Erectile Function (IIEF) on frequency of penetration and maintaining an erection to complete intercourse. The weighted mean difference for the scores was in favour of the intervention group. In the seven trials that included scores for the IIEF erectile function domain, the weighted mean difference was 6.6, in favour of the intervention group. In four trials, men who took PDE-5 inhibitors had an average weighted mean difference of 26.7% more successful intercourse attempts than did control patients.

Headache was the most frequent adverse event, followed by flushing. Other symptoms reported were upper respiratory tract complaints, dyspepsia, myalgia, abnormal vision, and back pain. Mortality was not reported in any of the eight trials. Only one study reported treatment-related cardiovascular morbidity in the intervention arm. The 10 events recorded included 4 cases of chest pain, 2 of which were myocardial infarctions with documented ST elevation; 2 cases of congestive heart failure; and 2 cases of hypertension.

Further research is needed to assess the effects of PDE-5 inhibitors in diabetic women with sexual dysfunction, in uncontrolled diabetic patients with ED, and on the cardiovascular system in diabetic patients who are prone to coronary artery disease and may suffer silent ischaemia, the review noted.

The authors said it was unfortunate that no head-to-head comparisons among the three available PDE-5 inhibitors or between PDE-5 inhibitors and other treatment modalities were conducted, and they called for further research in these areas.