Case Study: Type 1 and Type 2, Too?

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Presentation

R.M. is a 17-year-old African-American girl with new-onset diabetes, presumed to be type 2 diabetes. She presented to her pediatrician during the winter months with the classic symptoms of polyuria and polydipsia. She reported weight loss over the preceding weeks, but was otherwise well. Her family history was positive for type 2 diabetes in grandparents and some distant relatives and negative for autoimmune diseases.

Physical examination revealed a blood pressure of 103/53 mmHg, pulse of 79, and temperature of 38°C. Her weight was 60 kg (132 lb, 50–75th percentile), height was 155 cm (61 inches, 10th percentile), and body mass index (BMI) was 25 kg/m^2 (85th percentile). She had acanthosis nigricans and was at Tanner V stage of sexual development.

Urinalysis revealed a glucose level of >1,000 mg/dl and ketones of 40 mg/dl. Her initial laboratory studies included a blood glucose measurement of 726 mg/dl, bicarbonate of 21 mmol/l (normal range 23–32 mmol/l), venous pH of 7.37, hemoglobin A_{1c} (A1C) of 8.6%, and C-peptide of 1.0 ng/ml (normal range 0.6–3.2 ng/ml).

R.M. was admitted to the hospital for subcutaneous insulin therapy, fluids, and diabetes education. She was discharged to her home on metformin, 500 mg twice daily, and a split-mixed insulin regimen of NPH and lispro at ~1 unit/kg/day, with two-thirds being taken in the morning and one-third in the evening. She was also started on a fixed carbohydrate, reduced-fat meal plan.

At her first follow-up visit 1 month later, R.M. was found to be positive for islet cell autoantibodies (ICAs), glutamic acid decarboxylase (GAD) antibodies, and ICA-512 antibodies. Her A1C was 7.8%. Her insulin doses had been slowly decreased, with glucose levels consistently <150 mg/dl and total daily insulin requirements of ~0.5 units/kg/day. Her metformin was discontinued given her positive antibody studies and near-euglycemic blood glucose range.

At another follow-up 3 months later, R.M. was still off metformin, and her blood glucose levels were in a euglycemic range on <0.4 units/kg/day (10 units of NPH with 4 units of lispro at breakfast and 6 units of NPH with 3 units of lispro at dinner). Her A1C was 5.9%. She had not required any adjustments for high blood glucose levels.

Questions

1. How does one distinguish between type 1 diabetes and type 2 diabetes?
2. When should autoantibodies be measured?
3. In patients who have type 1 diabetes with evidence of insulin resistance, what treatment options are available?

Commentary

Most practitioners today would have assumed that this adolescent had recent-onset type 2 diabetes. The risk factors include non-Caucasian ancestry, positive family history, presence of acanthosis in someone with an elevated BMI, and hyperglycemia without ketoacidosis.[1]

In the past, type 1 diabetes would account for the majority of diabetes seen in this age-group. Yet, the national obesity epidemic has changed the types of diabetes being seen, especially in pediatrics. The most recent National Health and Nutrition Examination Survey noted that 30% of adolescents are now overweight,[2] and there has been a commensurate rise in the number of cases of type 2 diabetes found in adolescents.[3] Recently, in a cohort of obese adolescents, 20% were noted to have impaired glucose tolerance, and 4% had undiagnosed type 2 diabetes.[4] In some pediatric diabetes practices, type 2 diabetes now accounts for 25–50% of the patient population, and this continues to increase.[1]

The incidence of type 2 diabetes in American adolescents is highest among African-Americans, Latinos, and Asians.[1] For the African American population, this increased risk for type 2 diabetes results at least in part from the fact that African-American prepubertal children and adolescents have greater insulin resistance than their Caucasian counterparts, even when matched for BMI.[5,6]

Given the increase of obesity in our society, we expect that many children who present with new-onset diabetes will have evidence of obesity and acanthosis, which are strongly suggestive of type 2 diabetes. Yet, rather than assume that they have type 2 diabetes, clinicians must test for autoantibodies to clarify the underlying etiology.

R.M. was found to have positive antibodies directed against the β-cells and thus, clearly, has autoimmune-mediated type 1 diabetes. However, she also has evidence of insulin resistance, which is found in type 2 diabetes. Some have referred to this condition as "double diabetes," or "type 1.5 diabetes."

Multiple studies have shown that up to 90% of new-onset type 1 diabetic patients will have evidence of at least one antibody at diagnosis, and ~40–50% will have two or more.[7] Tests for four autoantibodies are now available through commercial laboratories. The traditional assay to measure ICAs involves incubat-

ing a patient's serum with a section of normal pancreas and assessing reactivity via indirect immunoflurosence. The other three antibody tests now available are for GAD, ICA-512 (also known as IA-2 or tyrosine phosphatase), and insulin autoantibodies (IAAs). The IAA measurement must be obtained within 10 days to 2 weeks from the initiation of exogenous insulin therapy, because exogenous insulin may induce antibody positivity.

Although most patients with type 1 diabetes are autoantibody-positive, ethnicity confers notable differences and may make confirmation of type 1 diabetes more difficult. African-American adolescents with new-onset type 1 diabetes have up to a fourfold greater chance of exhibiting no autoantibodies compared to their Caucasian counterparts (17.4 vs. 4.6%, respectively).[8] Thus, African-American adolescents with type 1 diabetes may initially present as antibody-negative, which may prove misleading in making therapy decisions.

The presence of autoantibodies has important implications for patient care. In the U.K. Prospective Diabetes Study, subjects presumed to have type 2 diabetes, yet who were noted to have one or more autoantibodies, progressed more rapidly to β-cell failure and required insulin therapy.[9] Up to 90% of patients who were positive for ICA and GAD antibodies required insulin within 6 years.[9]

In this case, had one assumed that this was a case of type 2 diabetes and treated R.M. solely with metformin, the patient may have done well initially, during her honeymoon phase. However, she would have been at high risk for progression to diabetic ketoacidosis as her honeymoon period waned or when faced with an intercurrent illness or stress. Furthermore, intensive insulin therapy is one potential means to prolong the honeymoon phase and protect endogenous insulin secretion,[10] and she would have been denied this potential benefit.

Despite the evidence that R.M. has type 1 diabetes, we must return to considerations about type 2 diabetes.

Although she tested positive for autoantibodies, she did present with acanthosis nigricans, an elevated BMI, a positive family history, and was from a higher-risk ethnic group. If we had studied her formally, she would almost certainly have exhibited increased insulin resistance, and she may have ultimately developed type 2 diabetes later in life if she had not had earlier autoimmune destruction of her β-cells.

One question to consider is whether there is a role for insulin sensitizers in such a situation. Metformin may be a useful addition to insulin for adolescents with type 1 diabetes and insulin resistance.[11] Preliminary studies have found that metformin lowered A1C, decreased insulin dosage, and caused no weight gain in adolescents with type 1 diabetes and poor metabolic control.[11] Clinicians initiating such therapy must carefully inform the patient and family about the risks of lactic acidosis and the increased risk for hypoglycemia with combined therapy. Further studies with metformin and other insulin sensitizers (such as thiazolidinediones) are needed before this will become established therapy.

For R.M., we elected to continue her subcutaneous low-dose insulin regimen at 0.4 units/kg/day during the honeymoon phase, but we may consider adding metformin therapy in the future.

Clinical Pearls

- With the surge in obesity, we are witnessing a rise in type 2 diabetes, especially among children and adolescents. These patients often present in puberty, at a time of increased insulin resistance.
- All pediatric patients who are diagnosed with new-onset diabetes need antibody studies obtained to distinguish type 1 from type 2 diabetes in order to provide appropriate therapies. Autoantibodies may not always be positive in African Americans with new-onset type 1 diabetes.
- Patients who have type 1 diabetes and evidence of insulin resistance may benefit from the addition of metformin as an insulin-sensitizing agent. However, the use of metformin in these patients is still under investigation and has not yet gained approval from the Food and Drug Administration.

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