Like-Triple Diabetes as First Manifestation of MODY2 in an Overweight Teenager With Transient Multiple Antibodies

Anna Wędrychowicz,[1]
Małgorzata Stelmach,[1]
Krystyna Wyka,[2] *and Jerzy Starzyk*[1]

Diabetes Care 2014;37:e66–e67 | DOI: 10.2337/dc13-2075

Patients with heterozygous inactivating mutations in the gene encoding glucokinase, which causes type 2 maturity-onset diabetes of the young (MODY2), have mild fasting hyperglycemia that usually remains considerably stable during life and requires only diabetic diet as treatment. Atypical course of disease is uncommon.

An 11-year-old, prepubertal, Caucasian overweight boy (BMI 22.5 kg/m^2) with gynecomastia/steatomastia and diabetes was diagnosed on the basis of an oral glucose tolerance test without any typical symptoms (2-h blood glucose 215 mg/dL). Insulin levels were quite high (fasting 17.1 IU/mL, 2-h 114 IU/mL). Since 6 years of age he had been treated for Asperger syndrome, currently with risperidone. His family history was positive for diabetes in the previous three generations. At the time of diabetes diagnosis, dyslipidemia with elevated total cholesterol (212 mg/dL), triglycerides (150 mg/dL), and LDL cholesterol (133.1 mg/dL) was observed. Diabetes autoantibodies were significantly positive: islet antigen 2 antibodies (IA-2A) 46 units/mL (N <20), islet cell antibodies (ICA) 90 (N <0), glutamic acid decarboxylase antibodies (anti-GAD) 158.2 units/mL (N <9.1), and insulin autoantibodies (IAA) 11.3% (N <7). Heterozygosis for GCG/GAG mutation in the glucokinase gene was detected (data were from the patient's medical documentation from another medical center).

The patient was admitted to our department 2 years later with the goal of modifying his treatment that included insulin analogs, metformin, and glimepiride, but not risperidone. HbA_{1c} had been fluctuating from 5.4–6.5%. His current body weight was appropriate for his height (−7%). Puberty was Tanner stage III. Lipid profile was normal. Anti-GAD antibodies were negative 0.6 IU/mL. Five days after pharmacotherapy discontinuation, a glucagon stimulation test revealed high C-peptide levels (baseline 3.1 ng/mL, 6 min after 8.9 ng/mL). In the following 2 years of observation, the HbA_{1c} had not exceeded 6% (42 mmol/mol) on diet treatment only. Notably, 3.5 years after the first positive results, the patient's diabetes autoantibodies assessed by the same person in the same certificated laboratory were negative (IA-2A 2.07 units/mL, ICA 0, anti-GAD 3.5 units/mL). According to the Diabetes Antibody Standardization Program 2009/2nd Islet Autoantibody Standardization Program 2012, the disease sensitivity of the antibody was ICA 52–72.3%, GAD antibodies 68–82%, IA-2A 66–70%, and IAA 66%, while corresponding specificities were ICA 76–93.3%, GAD antibodies 75–94.4%, IA-2A 47.6–70%, and IAA 49.6%.

There are no data in the literature regarding significant high multiple islet antibodies that disappear without the development of type 1 diabetes. However, some studies have shown that the development of multiple islet autoantibodies is a critical step in pathogenesis and thus provides a robust and early marker for risk of disease progression (1). The data for prevalence of positive diabetes autoantibodies in MODY2 patients are scarce and vary between publications (<1−17%) (2,3). The significance of the presence of diabetes autoantibodies in these patients remains unclear.

Some MODY2 patients display peripheral insulin resistance that might result from interactions between the unbalanced glucose metabolism and susceptibility of gene(s) to low insulin sensitivity (4). In the present case, risperidone could have prominent side effects including weight gain and hyperprolactinemia that resulted in the development of gynecomastia and an insulin-resistant state. It was reported that metformin could be an effective attenuator of risperidone-induced insulin-resistant hyperglycemia and dyslipidemia (5).

In conclusion, the positive diabetes autoantibodies can be transient in MODY2 patients and are not markers of prediabetes. It is possible that autoantibodies titers are aggravated

[1]*Department of Pediatric and Adolescent Endocrinology, Polish-American Pediatric Institute, Medical College, Jagiellonian University, Krakow, Poland*
[2]*Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Lodz, Lodz, Poland*

Corresponding author: Anna Wędrychowicz, anna.wedrychowicz@uj.edu.pl.

by obesity or by other factors, such as drugs.

Acknowledgments. The authors of the article hereby thank Maciej Borowiec and Wojciech Młynarski from the Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Lodz, for their help in the patient's diagnostic process. Autoantibody analyses and genetic tests were performed in the Laboratory of Immunopathology and Genetics, Medical University of Lodz, Lodz, Poland.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.W. researched data and wrote and edited the manuscript. M.S. contributed to the discussion and reviewed the manuscript. K.W. researched data, measured diabetic autoantibodies, contributed to the discussion, and reviewed the manuscript. J.S. reviewed the manuscript. A.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Bingley PJ. Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab 2010;95:25–33
2. McDonald TJ, Colclough K, Brown R, et al. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet Med 2011;28:1028–1033
3. Schober E, Rami B, Grabert M, et al.; DPV-Wiss Initiative of the German Working Group for Paediatric Diabetology and. Phenotypical aspects of maturity-onset diabetes of the young (MODY diabetes) in comparison with type 2 diabetes mellitus (T2DM) in children and adolescents: experience from a large multicentre database. Diabet Med 2009;26:466–473
4. Clément K, Pueyo ME, Vaxillaire M, et al. Assessment of insulin sensitivity in glucokinase-deficient subjects. Diabetologia 1996;39:82–90
5. Adeneye AA, Agbaje EO, Olagunju JA. Metformin: an effective attenuator of risperidone-induced insulin resistance hyperglycemia and dyslipidemia in rats. Indian J Exp Biol 2011;49:332–338