The changing landscape of diabetes in Canadian children

A 15-year-old Hispanic male presents to your office with a one-week history of significant fatigue. He denies associated symptoms. His past medical history is unremarkable and his family history reveals type 2 diabetes (T2D) in both maternal and paternal grandparents. His mother has hypothyroidism. His weight and height are 65 kg and 159 cm, respectively, with a calculated body mass index of 25.7 kg/m^2 (93rd percentile; *z* score of 1.48). His physical examination is unremarkable. His complete blood count, liver function, renal function and thyroid function tests are normal. His random blood sugar is 10.5 mmol/L, prompting you to arrange an oral glucose tolerance test, which reveals a 2 h blood sugar of 14.3 mmol/L. After reading the recent CPSP resource article on unravelling nontype 1 diabetes mellitus (NT1DM) in childhood, you realize your patient could have early type 1 diabetes (T1D), T2D or a monogenic form of diabetes. What clinical features and investigations can help you differentiate between these different forms of diabetes?

LEARNING POINTS

DM classical presentations

- T1D: Acute onset of symptomatic hyperglycemia in the presence of mild ketosis or severe diabetic ketoacidosis, and evidence of pancreatic autoimmunity in a nonobese child.
- T2D: Incidental or symptomatic hyperglycemia in a child with risk factors for T2D (see below) in the absence of ketosis or pancreatic autoimmunity.
- Monogenic diabetes: A child of normal weight with a family history of diabetes affecting multiple generations in the absence of features of insulin resistance and pancreatic autoimmunity.

These 'classic' presentations are less common in the face of increasing rates of childhood obesity and associated insulin resistance. Clinical features differentiating T1D from NT1DM overlap, leading to difficulties in the classification of diabetes. Therefore, in any child presenting with hyperglycemia, a thorough history and physical examination is essential in identifying risk factors for NT1DM.

NT1DM risk factors

- For T2D:
  - Obesity (body mass index greater than the 95th percentile for age and sex),
  - A positive family history of T2DM,
  - Specific ethnic backgrounds (Aboriginal, African or Caribbean, Hispanic and Asian),
  - Insulin resistance evidenced by the presence of acanthosis nigricans and/or polycystic ovarian syndrome, and/or hypertension, or
  - Exposure to gestational diabetes, intrauterine growth restriction, or large for gestational age.
- For monogenic diabetes:
  - Children with mild hyperglycemia in the absence of ketosis (suggestive of specific but not all types of monogenic diabetes),
  - A strong family history of diabetes with an autosomal dominant pattern of inheritance, or
  - Infants younger than six months of age diagnosed with diabetes, irrespective of family history.
- Other clues for NT1DM:
  - Minimal or no insulin requirement a year after diagnosis with a normal or near normal hemoglobin A1c level (4% to 6%), or
  - The presence of a syndrome known to be associated with T2DM, such as Prader-Willi syndrome.

In the presence of these risk factors, further investigations may be performed to facilitate the classification of diabetes in a child with hyperglycemia, including:

- Insulin and C-peptide levels:
  - May be elevated in T2D. Acute, severe hyperglycemia results in 'beta cell toxicity' and, therefore, insulin or C-peptide levels may initially be low in these patients. Insulin or C-peptide levels are a more useful measure after treatment has been initiated and glycemic control achieved.
- Markers of pancreatic autoimmunity (islet cell antibodies, glutamic acid decarboxylase antibodies, insulin autoantibodies and tyrosine phosphatase-like protein autoantibodies:
  - These are often absent in T2DM, monogenic diabetes and medication-induced diabetes.
- Genetic testing:
  - To identify specific mutations linked to monogenic forms of diabetes.

Some of these investigations, such as genetic testing for monogenic diabetes, are only available in research laboratories, and thus referral to a tertiary care, paediatric diabetes health care team may be necessary to obtain these confirmatory tests.

The identification of risk factors for NT1DM and, specifically, T2DM should help paediatricians in choosing further investigations to clarify the type of diabetes. This is very helpful clinically in guiding therapeutic decisions.

NT1DM study

- In the first year of NT1DM, nationwide surveillance in children zero to 17.9 years of age through the CPSP, in collaboration with the National Research System of the College of Family Physicians of Canada, resulted in 110 confirmed cases of NT1DM.
- Surveillance is continuing for another year to enhance data collection. Defining the existing spectrum of diabetes through epidemiological population-based studies will provide a baseline incidence estimate for future comparison. The research team thanks all of the physicians who have continued to support this important research.
- Join us at the Canadian Paediatric Society Annual Conference, June 2007, for a seminar on study results describing the changing landscape of diabetes in Canadian children.

The Canadian Paediatric Surveillance Program (CPSP) is a project of the Canadian Paediatric Society, which undertakes the surveillance of rare diseases and conditions in children. For more information, visit our Web site at <www.cps.ca/cpsp> or <www.cps.ca/pcsp>. Accepted for publication April 24, 2007