RESOURCES

Unraveling non-type 1 diabetes mellitus in childhood

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Recently, diabetes mellitus in children has evolved to a more complex differential diagnosis. Although type 1 diabetes mellitus remains the most common diagnosis, newly recognized forms of diabetes have emerged and are classified as "non-type 1 diabetes mellitus" (NT1DM). They comprise type 2 diabetes mellitus, secondary diabetes including medication-induced (e.g., steroids, L-asparaginase, tacrolimus), and monogenic forms of diabetes. This resource article will guide clinicians in understanding the pathophysiology, clinical presentation and diagnostic evaluation of NT1DM.

What are the pathophysiological mechanisms of NT1DM?

Type 2 diabetes mellitus (T2DM)

In the normoglycemic, insulin-sensitive individual, there is a precise balance between insulin secretion and insulin sensitivity. In the insulin-resistant individual, insulin secretion increases to compensate for decreased insulin sensitivity, maintaining normoglycemia. In T2DM, progressive beta cell failure leads to insufficient insulin secretion to compensate for insulin resistance resulting in hyperglycemia. Data on the pathophysiology of T2DM in children are sparse. The progression from normal glucose tolerance to T2DM in children has not been well studied. However, in one American cohort of 117 obese children and adolescents followed over 20 months, 10% of subjects with baseline normoglycemia developed impaired glucose tolerance (IGT) and 24% of subjects with IGT developed overt T2DM.[1]

Medication-induced diabetes mellitus (DM)

There is paucity of data in regards to DM secondary to medical therapy in childhood. Studies of post-renal transplant paediatric patients have shown medical therapy, most commonly associated with glucocorticoids, can result in severe hyperglycemia requiring insulin therapy.[2] Chemotherapeutic agents (e.g., L-asparaginase), and immunosuppressants (e.g., cyclosporine and tacrolimus) have also been implicated. Hyperglycemia results from a combination of direct pancreatic beta cell toxicity, interference with insulin secretion and induction of insulin resistance. Medications used to treat central nervous system disorders, such as atypical antipsychotics and anti-seizure medications, cause increased weight gain, increased insulin resistance, and in the most severe cases, diabetes.[3,4]

It is unclear whether those who develop hyperglycemia while taking diabetogenic medications are at higher risk for the development of T2DM in adolescence or early adulthood. Additionally, drug-induced DM during childhood may be increasing as a consequence of rising rates of obesity, insulin resistance and a lower threshold for hyperglycemia.

Monogenic diabetes

It has been estimated that monogenic forms of diabetes account for 1–5% of all cases of diabetes.[5] Recognition of this entity as an important cause of childhood DM has improved substantially over the last decade with the isolation of six causative gene mutations important in insulin and glucose regulation and pancreatic beta cell function.[6] Hyperglycemia in monogenic forms of diabetes, previously known as maturity-onset diabetes of the young (MODY), varies depending on the degree of dysfunction at the level of the pancreatic beta cell. Severity of the disease ranges from mild hyperglycemia requiring no therapy (e.g., glucokinase mutation) to significant hyperglycemia with requirement for early treatment with insulin (e.g., hepatic nuclear factor [HNF] 1α mutation).[7] The HNF mutations described initially in European people in the last decade are characterized by an autosomal dominant inheritance (single copy) of an insulin secretory defect that causes severe hyperglycemia but rarely diabetic ketoacidosis.[6]

The unique single nucleotide polymorphism (SNP-G319S) in the HNF 1α gene identified in the Oji-Cree of northwestern Ontario and Manitoba has provided new insights into the potential pathophysiology of the HNF mutations.[8] The G319S polymorphism causes an insulin secretory defect in vitro.[8] In the Oji-Cree population, one copy of the allele is associated with early-onset diabetes only in the presence of obesity, but two copies of this allele (homozygous) are associated with diabetes in adolescence.[8] This is also a plausible explanation as to why T2DM in Oji-Cree children was described 10 years earlier in Manitoba and why the incidence continues to be higher than anywhere else in Canada.

What is the clinical presentation of NT1DM?

The clinical presentation of NT1DM in children is symptomatic or incidental hyperglycemia. Symptoms may include polyuria, polydypsia, fatigue, weight loss, headache, and/or vaginal candidiasis. The diagnosis of diabetes is based on the Canadian Diabetes Association Guidelines.[9]

Differentiating between type 1 and NT1DM can be challenging.

- T1DM classically presents with acute onset of symptomatic hyperglycemia in the presence of mild ketosis or severe diabetic ketoacidosis and evidence of pancreatic autoimmune markers in a non-obese child.
- T2DM, based on clinical experience in the adult population, typically presents as incidental or symptomatic hyperglycemia in the absence of ketosis or pancreatic autoimmunity. Interestingly, studies in children with T2DM report that 20–25% of children may present with ketosis or in the

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most severe cases, diabetic ketoacidosis.[10] Furthermore, some studies have shown the presence of pancreatic autoimmune markers in children with a clinical diagnosis of T2DM.[11] The clinical significance of these auto-antibodies is yet to be elucidated.

- Medication-induced diabetes is diagnosed when hyperglycemia develops following the initiation of medical therapy with a known diabetogenic medication, including glucocorticoids, L-asparaginase, cyclosporine, tacrolimus, atypical antipsychotics or anticonvulsants.
- Monogenic diabetic patients generally have a strong family history of diabetes affecting multiple generations, a classically normal weight, and do not have features of insulin resistance or evidence of pancreatic autoimmunity.

With increasing rates of childhood obesity and associated insulin resistance, clinical features differentiating T1DM and NT1DM overlap, leading to difficulties in the classification of diabetes and choice of therapeutic regimen.

How to confirm the diagnosis of NT1DM?

In any child presenting with hyperglycemia, it is important to conduct a thorough history and physical exam to identify the presence of risk factors for NT1DM.

- T2DM risk factors include obesity (body mass index >95th percentile for age and gender), a positive family history of T2DM, specific ethnic backgrounds (Aboriginal, African/Caribbean, Hispanic, Asian), insulin resistance evidenced by the presence of *acanthosis nigricans* and/or polycystic ovarian syndrome, puberty, and exposure to gestational diabetes or intrauterine growth restriction.
- Risk factors for monogenic diabetes include children with mild hyperglycemia in the absence of ketosis and a strong family history of diabetes with an autosomal dominant pattern of inheritance.
- Other clues for NT1DM include minimal or no insulin requirement a year after diagnosis with a normal or near normal hemoglobin A1c level (4–6%), and 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 done to facilitate the classification of diabetes in a child with hyperglycemia, including:

- Insulin and C-peptide levels, which are elevated in T2DM. Of note is that acute, severe hyperglycemia results in “beta cell toxicity” and, therefore, insulin or C-peptide levels may initially be low in these patients and are a more useful measure after treatment has been initiated and glycemic control achieved.

- Markers of pancreatic autoimmunity (islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GADA), insulin auto-antibodies (IAA), and tyrosine phosphatase-like protein auto-antibodies (IA-2∀), which are present in T1DM and 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; thus, referral to a tertiary care paediatric diabetes health care team may be necessary to obtain these confirmatory tests.

Why is it important to make the right diagnosis?

Differentiating T1DM from NT1DM has become progressively more challenging, particularly in the severely symptomatic child. For example, an acutely hyperglycemic child diagnosed with T1DM who then demonstrates low insulin requirements and a near-normal hemoglobin A1C more than one year after diagnosis may be suspected to have monogenic (if he/she is lean) or T2DM (if he/she is obese). In the case of suspected T2DM, the treatment regimen should include a strong focus on lifestyle modification in addition to insulin therapy and/or oral insulin sensitizing agents such as metformin. Alternatively, the lean child with a very strong family history of T2DM requiring minimal therapy may have monogenic diabetes with family members being misclassified as having T2DM. Patients with confirmed hepatic nuclear factor-1α mutations have been shown to be very sensitive to oral sulfonylureas. Therefore, a revised diagnosis from T1DM to monogenic diabetes can drastically change the therapeutic approach from subcutaneous insulin injections to a simpler regimen of oral sulfonylureas for the patient, and potentially for other affected family members as well. Finally, individuals with medication-induced diabetes may be at greater risk for the development of T2DM and therefore warrant periodic assessment for diabetes. Early identification, initiation of lifestyle modification and treatment of these potentially high-risk children may significantly reduce future morbidity from diabetes-related complications.

The identification of risk factors for NT1DM and specifically T2DM should motivate paediatricians to seek further investigations that will clarify the pathophysiological mechanism underlying hyperglycemia and subsequently guide one's therapeutic choice. Furthering our knowledge through population-based studies on the epidemiology of NT1DM and T2DM in Canadian children will help define the existing spectrum of diabetes and provide a baseline incidence estimate for future comparison.

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Quiz

1. **Drug-induced diabetes is most commonly associated with glucocorticoids. Another medication associated with drug-induced diabetes is:**
   a) Sulfonylureas
   b) Ritalin
   c) Atypical antipsychotics
   d) Metformin
   e) All of the above

2. **A lean child presenting with mild hyperglycemia, no ketosis, and a strong family history of diabetes in an autosomal-dominant pattern likely has:**
   a) Type 2 diabetes
   b) Type 1 diabetes
   c) Monogenic diabetes
   d) Drug-induced diabetes
   e) Stress hyperglycemia

3. **Which of the following is NOT a clinical clue for non-type 1 diabetes?**
   a) Minimal or no insulin requirement one year after diagnosis
   b) Signs of insulin resistance
   c) A normal or near normal A1c (4–6%) level, one year after diagnosis
   d) Acute hyperglycemia and diabetic ketoacidosis
   e) Recent initiation of glucocorticoids

4. **Risk factor(s) for type 2 diabetes mellitus include:**
   a) Obesity
   b) Puberty
   c) A history of intrauterine growth restriction
   d) Asian ethnic background
   e) All of the above

5. **Investigation(s) that may help in the classification of diabetes mellitus in children include:**
   a) Insulin levels
   b) C-peptide levels
   c) Markers of pancreatic autoimmunity
   d) Genetic testing
   e) All of the above

Answers:
1-c, 2-c, 3-d, 4-e, 5-e

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Appendix