Is it Type 1 or Type 2 or MODY??
Various types of Diabetes in children & adolescents

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Objectives

- Introduction to various types of diabetes in children.
- Characters of type 1 diabetes.
- Characters of type 2 diabetes.
- Characters of MODY diabetes.
- How to distinguish between various types of diabetes.

Pediatric Diabetes

Is the second most common chronic illness of childhood

ADA Classification of diabetes in children2020

Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
A. Immune-mediated
B. Idiopathic
Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
Other specific types
A. Genetic defects of beta cell function
1. Chromosome 12, HNF-1-alpha (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4-alpha (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1-beta (MODY5)
6. Chromosome 2, NeuroD1 (MODY6)
7. Mitochondrial DNA
8. Others
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes

Type 1 Diabetes in children

- Type 1 diabetes is characterized by destruction of the pancreatic beta cells, leading to absolute insulin deficiency.
- Usually due to autoimmune destruction of the beta cells (type 1A).
- Testing for islet cell antibodies (ICA), antibodies to GAD 65; insulin; IA-2 ; and zinc transporter ZnT8 , essential for establishing the diagnosis.
- However, the absence of pancreatic autoantibodies does not rule out the possibility of type 1 diabetes (type 1b).
- Idiopathic “type 1b ” occurs in some patients with absolute insulin deficiency, have no evidence of autoimmunity and have no other known cause for beta cell destruction.

Type 2 diabetes mellitus in children & adolescents

- Is by far the most common type of diabetes in adults.
- Characterized by hyperglycemia & variable degrees of insulin resistance.
- It is a common disorder whose prevalence rises markedly with increasing degrees of obesity.
- Insulin resistance can arise through genetic & environmental influences.
- Type 2 diabetes is on the increase in all age groups, even among children above age of 10 and adolescents.
- Because of the relatively recent recognition of this type, many children with new onset T2DM may be misclassified as having T1DM.

- Patients with type 2 diabetes typically present with hyperglycemia, although ketoacidosis may occur.
- Diabetic ketoacidosis (DKA) in type 2 diabetes occurs by several mechanisms, similar to those in type 1 diabetes.
- While it is known that diabetic ketoacidosis (DKA) can occur in the presence of complete insulin deficiency and it is not a typical feature of type 2 diabetes, some patients with type 2 diabetes develop DKA under certain circumstances (usually severe infection or other illness).

Distinguishing Type 1 Vs Type 2

- Autoantibodies, especially anti GAD (screening test) should be done in overweight or obese children / adolescents presenting with apparent type 2 diabetes.
- Measurements of serum insulin (prior starting insulin) & c-peptide is important to differentiate between the 2 types.
- Given the risk of ketoacidosis, insulin should be started in children/ adolescent suspected to have type 1 or type 2 diabetes, who is catabolic (weight loss or dehydration in the setting of hyperglycemia), or who has evidence of increased ketogenesis (ketonuria or acidosis) and continue until we have antibody results.

Type 1 Vs Type 2 in children &adolescents

Type 1	Type 2
Sudden onset	Gradual / insidious onset
Moderate to severe symptoms	Mild or even no symptoms, or discovered by screening
Initially, positive history of marked weight loss	Usually no history of weight loss
Thin children	Over weight / obese
Autoimmune β – cell destruction	Insulin resistance
No acanthosis nigricans	Acanthosis nigricans positive
Ketosis -prone	Ketosis may happen
Autoantibodies positive	Autoantibodies negative
Low insulin / c- peptide	Initially normal/ high insulin & c-peptide
Life threatening if not treated with insulin	Could be managed with diet/ exercise

Maturity onset diabetes of the young (MODY)

Estimated prevalence worldwide is 2 to 5 % of all patients with diabetes

Maturity-onset diabetes of the young (MODY)

- It was first reported in 1974.
- A heterogeneous disorder characterized by non-insulin-dependent diabetes with onset younger of 25 years with autosomal dominant transmission and lack of autoantibodies.
- Many patients are misclassified as having either type 1 or 2 diabetes.
- Usually average body built, however, 15–25% of newly diagnosed with T1DM or MODY patients may be obese!
- To improve the prognosis of MODY, it is important to identify the affected subjects as early as possible.
- Specific molecular analyses are available to predict the clinical disease course and offer the most appropriate treatment.

Maturity onset diabetes of the young (MODY)

- Approximately 80% of patients with MODY may be misdiagnosed with type 1 or type 2 diabetes mellitus at diagnosis.
- Current medical reports indicated a delay of approximately 15 years from the diagnosis of diabetes to the genetic diagnosis of MODY.
- Several different genetic abnormalities have been identified, each leading to a different subtype of disease.
- To date, mutations associated with MODY have been reported in least 14 different genes
- Six genes encoding major subtypes, while, MODY subtypes 7–14, responsible for mild subtypes.

Maturity onset diabetes of the young: More commonly identified gene mutations

Type	Genetic defect	Frequency	Beta cell defect	Clinical features	Risk of microvascular disease	Optimal treatment
1	Hepatocyte nuclear factor-4-alpha	<10%	Reduced insulin secretory response to glucose	Normal renal threshold for glucose	Yes	Sulfonylureas
2	Glucokinase gene	15 to 31%	Defective glucokinase molecule (glucose sensor), increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion	Mild, stable, fasting hyperglycemia, often diagnosed during routine screening. Not progressive.	Generally no	Diet
3	Hepatocyte nuclear factor-1-alpha	52 to 65%	Abnormal insulin secretion, low renal threshold for glucose	Low renal threshold for glucose, +glycosuria	Yes	Sulfonylureas

Maturity onset diabetes of the young: More commonly identified gene mutations

4	Insulin promoter factor 1	Rare	Reduced binding to the insulin gene promoter, reduced activation of insulin gene in response to hyperglycemia	Rare, pancreatic agenesis in homozygotes, less severe mutations result in mild diabetes	Yes	
5	Hepatocyte nuclear factor-1-beta	Rare		Pancreatic atrophy, renal dysplasia, renal cysts, renal insufficiency, hypomagnesemia	Yes	Insulin
6	Neurogenic differentiation factor-1	Rare	Pancreatic development		Yes	Insulin

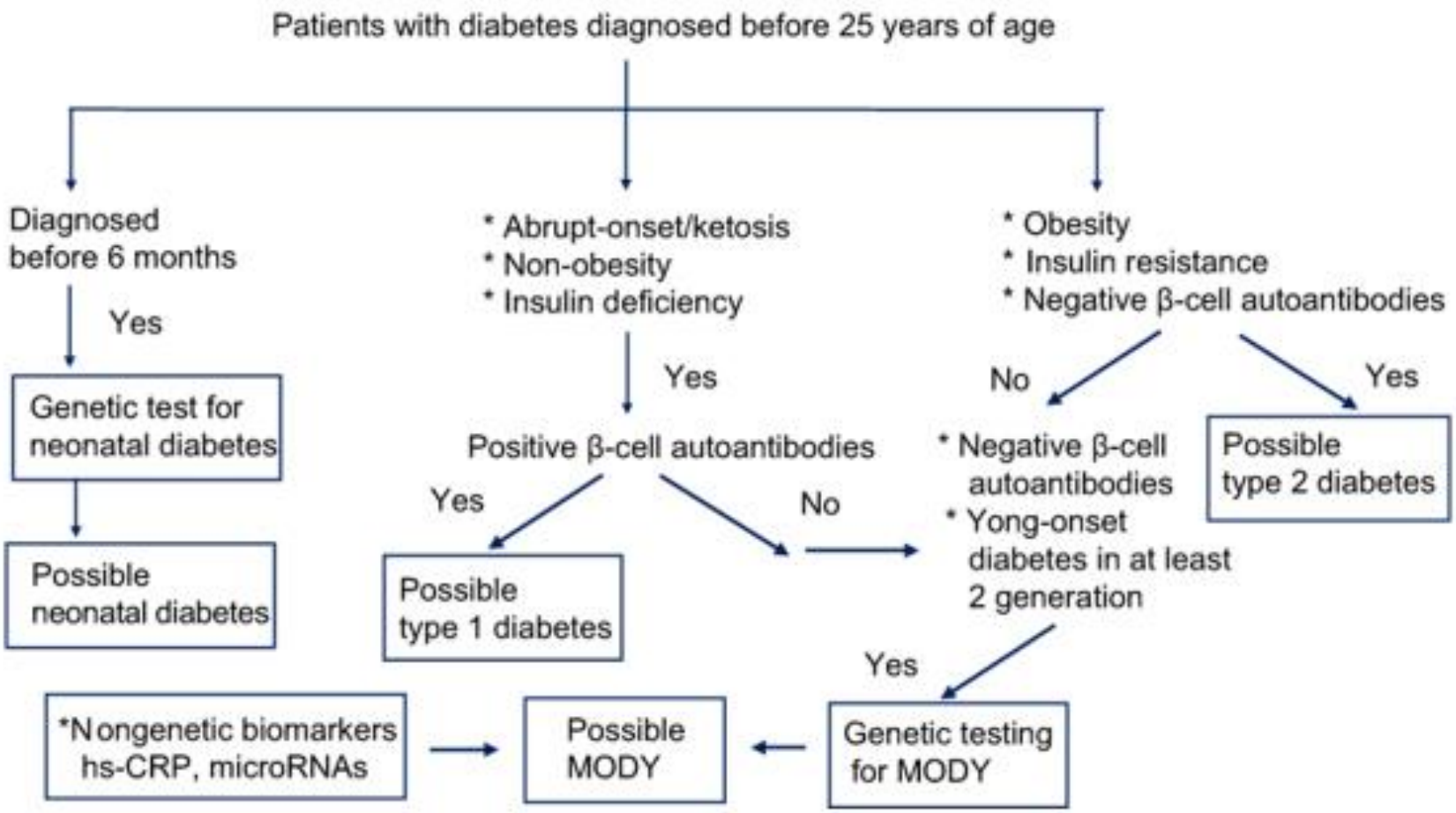
Indications for genetic testing

- It is important to distinguish MODY from type 1 & type 2 diabetes because the treatment & risk for diabetes complications varies with the underlying genetic defect.
- Patients with MODY due to *HNF1α* or *HNF4α* mutations are frequently misdiagnosed as having insulin requiring type 1 diabetes because they present at an early age and are not obese.
- To perform genetic testing for MODY when there is a high index of suspicion (familial diabetes with autosomal dominant pattern of inheritance (>2 generations), onset <25 years, nonobese, negative islet autoantibodies).

Summary & Recommendations

Clinical features distinguishing type 1 diabetes, type 2 diabetes, and maturity onset diabetes of the young

Clinical features	Type 1 diabetes mellitus	Type 2 diabetes mellitus	MODY
Age of diagnosis (years)	Majority <25, but may occur at any age	Typically >25 but incidence is increasing in adolescents, paralleling increasing rates of obesity in children and adolescents*	<25
Weight	Usually thin, but with obesity epidemic overweight and obesity at diagnosis becoming more common	>90% at least overweight	Similar to general population
Autoantibodies	Present	Absent	Absent
Insulin dependent	Yes	No	No
Insulin sensitivity	Normal when controlled	Decreased	Normal (may be decreased if obese)
Family history of diabetes	Infrequent (5 to 10%)	Frequent (75 to 90%)	Multigenerational, ie, >2 generations
Risk of diabetic ketoacidosis	High	Low	Low


Patients with diabetes diagnosed before 25 years of age
Diagnosed before 6 months
Yes
Genetic test for neonatal diabetes
Possible neonatal diabetes
* Abrupt-onset/ketosis
* Non-obesity
* Insulin deficiency
Yes
Positive β-cell autoantibodies
Yes
Possible type 1 diabetes
No
* Obesity
* Insulin resistance
* Negative β-cell autoantibodies
No
Yes
Possible type 2 diabetes
* Negative β-cell autoantibodies
* Yong-onset diabetes in at least 2 generation
Yes
Genetic testing for MODY
Possible MODY
*Nongenetic biomarkers hs-CRP, microRNAs

- Type 1 diabetes is characterized by autoimmune destruction of the pancreatic beta cells.
- Type 2 diabetes is characterized by variable degrees of insulin resistance.
- It is occasionally difficult to distinguish between type 1 and A typical presentations of type 2 diabetes.
- Measurement of 2-3 autoantibodies when the diagnosis of type 1 or type 2 diabetes is uncertain by clinical presentation.
- MODY, is a clinically heterogeneous disorder characterized by noninsulin-dependent diabetes diagnosed at a young age (<25 years) with autosomal dominant transmission and lack of autoantibodies.

- It is classified by the underlying genetic defect.
- The diagnosis of MODY is made by performing diagnostic genetic testing by direct sequencing of the gene, primarily for mutations in hepatocyte nuclear factor-4- *α* (*HNF4A*), hepatocyte nuclear factor-1- *α* (*HNF1A*), & glucokinase (*GCK)* gene.
- To perform genetic testing for MODY when there is a high index of suspicion (familial diabetes with autosomal dominant pattern of inheritance (>2 generations), onset <25 years, nonobese, negative islet autoantibodies).




Thanks