Changing picture of diabetes classification: a case report

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Making a clear distinction in the diagnosis of diabetes is important to ensure the patient is provided with appropriate treatment and counselling about future management. The use of immunological and genetic investigations can help aid diagnosis. We report a paediatric case who presented with classic features of type 2 diabetes and low levels of GAD autoantibody, whose symptoms and glucose levels resolved with weight reduction. Twenty months later she had begun to display symptoms suggestive of type 1 diabetes and was positive for three auto-antibodies, therefore insulin treatment was started. Non-insulin-dependent adults aged over 30 years and positive for auto-antibodies have been referred to as having latent autoimmune diabetes of adults (LADA), and have high likelihood of early progression to insulin requirement; however, it has been suggested they be recategorised as type 1 diabetes as they will ultimately need insulin, even if their disease progression is relatively slow.

It is important to make a clear distinction when diagnosing the type of diabetes a patient presents with to ensure that appropriate treatment and counselling for future management are given. The distinction between type 1 diabetes (T1D) and type 2 diabetes (T2D) may initially seem clear, as key characteristics – the patient's weight and age, symptoms such as polyuria and polydipsia, the presence of ketosis or physical symptoms such as acanthosis nigricans – can help separate the two (Ramachandra et al, 2009). However, patients often present in a way in which the two types of diabetes overlap. The prevalence of childhood obesity is increasing internationally, and this can mislead when clinically considering which is the most likely type of diabetes. According to Couper et al (2014), insulin resistance is present in up to a third of children presenting with overweight or obesity at T1D diagnosis.

The use of immunological and genetic investigations can help aid diagnosis (Ramachandra et al, 2009). The presence of beta-cell specific auto-antibodies indicates that an autoimmune process behind the beta-cell depletion is likely and usually suggests T1D. However this is not absolute. T1D may present with negative auto-antibodies at diagnosis. The absence of antibodies therefore does not rule out T1D if the clinical picture is classical. Maahs et al (2010) recommended subclassifying T1D into type 1A (typical, autoimmune-mediated) and type 1B (idiopathic, more commonly seen in specific ethnic groups and less frequently in Caucasian patients). The absence of auto-antibodies suggests an alternative form of diabetes, such as T2D or maturity-onset diabetes of the young (MODY), should be considered (Craig et al, 2014), see *Table 1*. It should be noted, however, that patients with features typical of

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Article points

1. In this case report, the diagnosis of diabetes type changed with disease progression, which could be consistent with the patient experiencing more than one diabetes type over a short period of time or akin to early-onset latent autoimmune diabetes in adults (LADA).
2. In cases where the features change from those typical of type 2 to type 1 diabetes, in the presence of auto-antibodies, clinicians should ensure the patient receives adequate monitoring and counselling, as well as early insulin initiation when needed.
3. Questions remain about LADA as a diagnosis.

Key words

- Diabetes classification
- Beta-cell auto-antibodies
- Insulin resistance
- Latent autoimmune diabetes in adults

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Table 1. Characteristics of the different types of diabetes at presentation (Carlsson et al, 2007; Craig et al, 2014; International Society for Pediatric and Adolescent Diabetes, 2018).

Characteristic	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes (MODY types)	LADA
Symptoms	Typical: • Polyuria • Polydipsia • Weight loss • Fatigue	Symptomatic (30–50%): • Polyuria • Fatigue Asymptomatic: incidental diagnosis	May be symptomatic; symptoms may depend on the type of monogenic diabetes Asymptomatic: incidental diagnosis	Initially more type 2 features but can progress to type 1 symptoms
BMI at diagnosis	Typically healthy or low; with increasing population BMI, more are classed overweight	Usually raised (approximately 90% are clinically obese)	Consistent with the general population	Consistent with the general population
Associated conditions	Other autoimmune conditions, such as thyroid (Hashimoto's or Graves' disease), adrenal (Addison's disease), vitilligo or coeliac disease	Acanthosis nigricans Hypertension Polycystic ovarian syndrome Specific syndromes, such as Klinefelter, Bardet Biedl, Prader–Willi, Alström	Depends on type; seek history of: Neonatal hypoglycaemia Eye/kidney disease Learning difficulty Deafness	Other autoimmune conditions
Age at diagnosis	Most common to present in children >12 months, up to young adult age	Usually post puberty; very rare in children <10 years	Often post puberty Consider in all 'neonatal' diabetes diagnoses <12 months	At least 30 years old (current definition)
Family history of diabetes	First-degree relative with type 1 diabetes in around 4% cases	Approximately 80% have a parent with diabetes	Usually present, although may not have been diagnosed as monogenic diabetes. Often over several generations, diabetes onset in young adulthood	Often present; associated with increased prevalence of LADA
Biochemical features				
Presence of ketones	Common at diagnosis (approximately 30% present with diabetic ketoacidosis)	Uncommon but may be present	Usually absent; may be present in neonatal diabetes/specific ketosis-prone atypical diabetes	Unlikely; ketosis risk increases as beta-cell function declines
C-peptide level	Low at diagnosis and falls over time	Often raised at diagnosis (indicator of insulin resistance)	Usually detectable >5 years after diagnosis (can be used to differentiate from type 1 diabetes)	Fasting C-peptide lower in LADA than in type 2 diabetes
Autoantibodies	Positive for at least one autoantibody (GAD/IA2/IAA) in around 80% of cases. Adding ZnT8 to the panel, >94% are positive	Typically absent	Absent	Presence required for classification

LADA = latent autoimmune diabetes of adults; MODY = maturity-onset diabetes of the young

T2D may be positive for diabetes auto-antibodies: 15–40% of paediatric patients diagnosed with T2D are autoantibody-positive, including those not requiring insulin for over 1 year (Reinehr, 2013). Non-insulin dependent adults positive for auto-antibodies have been referred to as having latent autoimmune diabetes of adults (LADA). For a diagnosis of LADA, patients must be positive for one or more of the four antibodies commonly found in T1D, be aged at least 30 years and not be treated with insulin within the first 6 months after diagnosis (Ramachandra et al, 2009). The presence of auto-antibodies may be an indication of risk that the patient will more rapidly develop a need for insulin (Zeitler et al, 2014; International Society for Pediatric and Adolescent Diabetes, 2018).

We discuss the case of a paediatric patient whose diabetes classification changed over time. We discuss the clinical management, possible explanations for changing classification, and mention parallels with latent autoimmune diabetes in adults (LADA). We conclude with clinical learning points to take from this case.

Case study

A 12-year-old girl was referred for review due to a random blood glucose finding of 10.9 mmol/L during primary care investigations for fatigue, menorrhagia and abdominal pains. She had a high BMI of 30 and a past medical history of congenital left-sided sensorineural hearing loss. Her family history included two great uncles with T1D and a grandparent with T2D.

At initial review, the patient was asymptomatic and a urine dip was negative for ketones and glucose. On examination she had acanthosis nigricans in her groin and axilla. Investigations found:

- HbA_{1C}: 53 mmol/mol (7%)
- Insulin: 20 mU/L
- HOMA-IR (homeostatic model assessment for insulin resistance): 6.5
- Oral glucose tolerance test: 7.5 mmol/L at 0 hours and 17.9 mmol/L at 2 hours.

C-peptide was not measured at this point. Her HOMA-IR result indicated increased insulin resistance, as the upper limit of the normal range is 4.5 in pubertal children. The patient's auto-antibodies were weakly positive for GAD 32 but negative for IA2 and ZnT8 antibodies. It was therefore concluded that she had T2D. The patient's diabetes was managed with diet and exercise to achieve weight loss, and metformin 250 mg once daily commenced.

Four months on from diagnosis, the patient had lost 10 kg following her diet and exercise plan, which equated to 13% weight loss, and her BMI had dropped to 24.9. Her HbA_{1C} was 31 mmol/mol (5%). At subsequent reviews she continued to lose weight, and her HbA_{1C} remained within non-diabetic range, therefore her metformin was stopped and she remained in apparent remission. The patient's classification was changed to 'transient hyperglycaemia of unknown cause' and she was given advice to remain alert to symptoms of diabetes and counselled that she would remain at a higher risk of diabetes in the future.

Eighteen months after her first presentation, she reported fatigue, mild polyuria, polydipsia and recent weight loss. Her HbA_{1C} had increased to 72 mmol/mol (8.7%) and she was negative for ketones. The results of oral glucose tolerance tests were higher than on first presentation (12.7 mmol/L at 0 hours and 23.4 mmol/L at 2 hours). Her C-peptide level was 483 pmol/L, which is at the lower end of the normal range for healthy normoglycaemic individuals (350–1800 pmol/L). At this time, T2D recurrence was presumed in view of the patient's previous insulin resistance and lack of ketones, and treatment with metformin was recommenced. The patient's autoantibody results were subsequently found to be positive for GAD 32, IA2 and ZnT8, in keeping with T1D and insulin was promptly started and metformin subsequently stopped. A year after diagnosis with T1D, her HbA_{1C} is 59 mmol/mol (7.5%).

Discussion

Our case included a number of features initially consistent with T2D:

- A high BMI
- No symptoms of polyuria/polydipsia
- Absence of ketones
- Acanthosis nigricans
- Negative results for IA2 and ZnT8 auto-antibodies
- Demonstrable insulin resistance.

"The presence of auto-antibodies may be an indication of risk that the patient will more rapidly develop a need for insulin."

Page points

1. Currently all young patients positive for auto-antibodies are considered at risk for future type 1 diabetes.
2. Patients with features suggestive of type 2 diabetes and auto-antibodies should be counselled about the risk of beta-cell destruction, type 1 diabetes and early insulin requirement.
3. In the presence of auto-antibodies, patients should be monitored for associated autoimmune conditions.

The weak presence of GAD antibody suggested the potential for autoimmune destruction, but was thought to be of doubtful significance. GAD antibody is present in around 20% of young people with T2D, and GAD-positive individuals seem to have no difference in C-peptide levels or predicted future need for insulin treatment compared to GAD-negative individuals (Dabelea et al, 2007; Bingley, 2010). In keeping with a diagnosis of insulin resistance, which is known to improve with weight loss, our patient went on to complete remission of biochemical measures of diabetes following weight reduction.

Our paediatric patient fulfilled the criteria for LADA apart from the age limit. Reinehr (2013) proposed that this type of presentation could be termed latent autoimmune diabetes mellitus in youth (LADY), and currently all patients positive for auto-antibodies are considered at risk for future T1D. Bingley (2010) discussed whether this specific patient group might benefit from a different management approach, but this has yet to be determined.

When our patient later presented with polyuria/polydipsia and a normal BMI, it could be argued that insulin be commenced pending her autoantibody results; however on the basis of her past history and known insulin resistance, metformin was restarted. Holding off insulin initiation increases the risk of developing ketosis, however this risk must be balanced against the potentially negative impact of a more prolonged admission to start insulin, if this is unnecessary. Individual circumstance will determine the choice made, but clinicians should sensitively share these uncertainties with the family and ensure they have an awareness of the symptoms of ketosis and remain in close contact until the antibody results are known.

There are two possible pathways for changes in the clinical phenotype of diabetes over time:

- A child or young person with features suggestive of T2D, but positive for one or more auto-antibodies, may be developing an autoimmune process and be at higher risk of early progression to insulin requirement. (This is highlighted for LADA in adults but is not described in 'LADY'. The clinician should remain alert to any positive antibody as a risk factor for future insulin requirement/the development of T1D features).
- Hyperglycaemia, whatever the primary cause, may exacerbate insulin resistance and reduce insulin secretion, leading to a requirement for insulin treatment.

In our case, while the patient was clearly insulin resistant at initial presentation, autoimmune or hyperglycaemia-mediated beta-cell destruction may have already been under way. Weight loss likely contributed to the short-term resolution of insulin resistance, with the subsequent start of an autoimmune process and deterioration of insulin secretion.

Conclusion

Patients do not always present with a clear type of diabetes. It is our opinion that for patients who have clinical features suggestive of T2D and who are positive for auto-antibodies, clinicians be alert to a greater risk of beta-cell destruction, T1D, and early requirement for insulin. Patients should be counselled about this risk and the associated symptoms. The monitoring frequency for these patients should be planned accordingly. The presence of auto-antibodies also indicates the need to monitor for associated autoimmune conditions; such monitoring is not indicated in antibody-negative T2D annual screening. ■

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