Unravelling the heterogeneity of non insulin dependent diabetes

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R Coll Physicians Lond 2000;34:332-5

Traditionally, non insulin dependent diabetes (NIDDM) was felt to be a distinct diagnosis both pathologically and clinically. Recently it has become clear that there is an expanding group of disorders with NIDDM, and the term type 2 diabetes is now reserved for those patients in whom a specific aetiological diagnosis cannot be made. A number of single gene defects cause isolated beta cell dysfunction, insulin resistance or syndromes that include diabetes. It is important to attempt to unravel this heterogeneous group because the precise diagnosis has implications for predicting disease progression and complications, individual treatment and the screening of family members. The definition of the specific aetiological disorders is primarily clinical, although confirmatory diagnostic laboratory tests are now available.

In this review, diabetes subgroups are divided clinically into those presenting with isolated diabetes (diabetes alone) and those with diabetes plus other features, usually as part of a syndrome complex (diabetes plus).

Diabetes alone

Type 2 diabetes is usually an insidious onset disease of the middle-aged or elderly, associated with obesity. In contrast, type 1 diabetes occurs in young people, and is associated with ketosis and rapid in onset. There is, however, a grey area where these distinctions become blurred, making diabetes classification difficult. It is now recognised that type 2 diabetes can present in early adulthood1 and, conversely, type 1 diabetes can present in the middle-aged and elderly (latent autoimmune diabetes of adulthood (LADA)).

In a young adult (<45 years) with slowly progressive onset of diabetes, three main differential diagnoses need to be considered (the clinical characteristics of these distinct groups are listed in Table 1):

- early-onset type 2 diabetes (EOD)
- latent autoimmune diabetes of adulthood (LADA)
- maturity onset diabetes of the young (MODY).

Early onset type 2 diabetes

EOD, at least in the early years, does not need insulin. Diabetes develops early (<45 years) due to increased genetic susceptibility: usually both parents are diabetic or have impaired glucose tolerance, and their offspring receive a 'double gene dose'1. Genetic factors also explain why EOD is common in populations with a high prevalence of diabetes (eg Asian). Most patients with EOD are obese, and this may be marked (body mass index (BMI) >35 kg/m2). They are often hypertensive and have dyslipidaemia which, combined with their long disease duration because of the early onset, puts them at high risk of micro- and macrovascular complications.

Table 1. Clinical characteristics of the differential diagnosis of young adults with non insulin dependent diabetes.

| Diabetes type | LADA | EOD | MODY |
|---------------|------|-----|------|
| Inheritance   | Polygenic | Polygenic | Monogenic autosomal dominant |
| Age of onset (years) | Usually >25 | 25-40 | <25 |
| Parents affected | 0 | 2 | 1 |
| Insulin treatment | Variable, usually months or years | Not initially | Not initially |
| GAD autoantibodies | Yes | No | No |
| Obesity | Rare | Common | Rare |

EOD = early onset type 2 diabetes; GAD = glutamic acid decarboxylase; LADA = latent autoimmune diabetes of adulthood; MODY = maturity onset diabetes of the young.
Latent autoimmune diabetes of adulthood

Sixty per cent of type 1 diabetes present after the age of 20, but the slow onset of LADA makes it hard to differentiate from type 2 diabetes\(^5\). The hallmark of LADA is an autoimmune process characterised by the presence of pancreatic autoantibodies, of which the most useful and robust are glutamic acid decarboxylase antibodies\(^5\). LADA patients frequently require insulin treatment early in their clinical course, but may not be insulin dependent years after diagnosis. They are younger and thinner than type 2 diabetic patients, without evidence of autoimmunity, and usually insulin deficient rather than insulin resistant\(^6\).

Maturity onset diabetes of the young

MODY is a group of autosomal, dominantly inherited, early onset NIDDM\(^6\) caused by a defect in beta cell function. It is thought to account for 1–2% of type 2 diabetes. Five types have currently been identified (Table 2). The two most common types result from mutations in the hepatocyte nuclear factor-1 alpha (HNF1\(\alpha\)) and the glucokinase genes\(^5\).

HNF1\(\alpha\) MODY is due to a progressive deterioration in beta cell function\(^6\). Under the age of 10 years most of these subjects have normal glucose tolerance. The mean age of diagnosis of diabetes is 22 years, commonly presenting with polyuria and polydipsia. Consistent with the deterioration in beta cell function, there is progressive deterioration in glucose tolerance, with increasing treatment requirements with time. Microvascular complications can develop, particularly retinopathy. Not surprisingly, a large number of HNF1\(\alpha\) MODY subjects have been labelled and treated as having either type 1 or type 2 diabetes. Specific features that should highlight the possibility of HNF1\(\alpha\) MODY include:

- an autosomal dominant family history
- normal BMI
- marked sensitivity to sulphonylurea medication (excellent glycaemic control on the lowest dose of sulphonylurea, or recurrent hypoglycaemia with sulphonylurea)
- low insulin requirements
- absence of ketosis.

Mutations in the glucokinase gene cause a defect in beta cell glucose sensing\(^5\). Thus, there is a resetting of the fasting glucose level at a higher baseline. Although the beta cell glucose threshold is reset, beta cell function is otherwise normal, so there is good response to a glucose challenge and often only a small increment (<3 mmol/l) following an oral glucose tolerance test. All patients have an elevated blood glucose from birth (6–8 mmol/l), with only mild deterioration over time but, because this elevation is only slight, most subjects are asymptomatic and diagnosis is usually made on routine screening, commonly during pregnancy. Microvascular complications are rare.

### Table 2. The different subtypes of maturity-onset diabetes of the young (MODY).

| MODY       | GCK | HNF1\(\alpha\) | IPF1 | HNF1\(\beta\) |
|------------|-----|---------------|------|---------------|
| 1          | 15  | 70            | <1   | 2             |
| 2          | Mild stable hyperglycaemia | Progressive deterioration in glycaemia |
| 3          | Birth | 12–28         | 14–20 | 12–28         |
| 4          | Low glucose rise on OGTT | Sulphonylurea sensitivity |
| 5          | Very rare | Common | ? | Yes |
|            | Usually none except in pregnancy | Progressive increase in requirements |
|            |                  | Sulphonylurea first-line after diet failure |

OGTT = oral glucose tolerance test.

Diabetes plus

Patients who have diabetes may have other coexistent conditions, but a proportion will have specific genetic syndromes. Some of the crucial characteristics and differential diagnosis of some of these syndromes are shown in Fig 1.

Diabetes and deafness

Maternally inherited diabetes and deafness (MIDD) is caused by a mutation in mitochondrial DNA (3243 tRNA\(^{m\text{et}}\)). The diabetes is a non insulin dependent type that usually presents before the age of 40 years; it is due to a defect in beta cell function with normal insulin sensitivity. The associated deafness is sensorineural and develops in most of
the diabetic subjects. Hearing loss is variable, but can require a hearing aid. In keeping with other mitochondrial disorders, MIDD may have other multi-organ features: for example, elevated serum lactate, neuromuscular and cardiac problems, pigmented retinopathy, and nephropathy with proteinuria.

Wolfram syndrome

A syndrome involving diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) is recessively inherited and results from a mutation in the transmembrane gene, WFS1. Presentation is usually in the first decade, with insulin dependent diabetes and optic atrophy. Diabetes insipidus and sensorineural deafness occur in the second decade, renal tract outflow problems in the third, and multiple neurological problems (including ataxia) in the fourth. Death usually follows respiratory failure due to brain stem atrophy, and few patients live beyond middle age.

*Diabetes plus severe obesity*

Obesity results in insulin resistance. A significant proportion of patients with type 2 diabetes are obese, with the associated insulin resistance contributing to their development of diabetes. There are well-defined genetic syndromes associated with severe obesity and diabetes. These patients frequently have acanthosis nigricans, the cutaneous marker of severe insulin resistance. The severe obesity related conditions, the key features of which are outlined in Table 3, include:

- Alstrom syndrome
- Bardet-Biedl syndrome
- Prader-Willi syndrome

*Diabetes plus severe insulin resistance*

Various clinical syndromes have been identified in which the key feature is severe insulin resistance. Many of them are caused by mutations in the insulin receptor gene. These syndromes have been reviewed elsewhere. In summary, they are:

- Leprechaunism, a congenital syndrome characterised by growth retardation, dysmorphic facies, severe insulin resistance and lipoatrophy.
- Rabson-Mendenhall syndrome, less severe than leprechaunism, with a longer life expectancy and less severe growth retardation. Clinical features include dystrophic nails and teeth, and precocious puberty.

**Fig 1. The crucial characteristics and differential diagnosis of ‘diabetes plus’**.
Table 3. Main subgroups of severe obesity and diabetes.

| Syndrome                                      | Alstrom          | Bardet-Biedel      | Prader-Willi       |
|----------------------------------------------|------------------|--------------------|-------------------|
| Genetics                                     | Autosomal recessive | Autosomal recessive | Usually de novo  |
| Unknown gene located on chromosome 2p       | Four unknown genes located on chromosomes 3, 11, 15, 16 | Similar phenotypes | Loss of paternally derived |
| Key features                                 | Retinitis pigmentosa | Retinitis pigmentosa | Neonatal hypotonia |
| Retinitis pigmentosa                        | Childhood obesity | Childhood obesity | Hyperphagia        |
| Childhood obesity                           | Acanthosis nigricans | Acanthosis nigricans | Childhood obesity |
| Acanthosis nigricans                        | NIDDM             | NIDDM              | Mental retardation |
| NIDDM                                        | Sensorineural deafness | Polyactyly        | Mental retardation |
| Sensorineural deafness                      | Hypogonadism      | Renal cysts        | NIDDM              |
| Other features                               | Renal failure     |                    | Short stature      |
| Cardiomyopathy                              |                    |                    | Small hands and feet |
| Nephropathy                                  |                    |                    | Hypogonadism       |
|                                              |                    |                    | Small external genitalia |

NIDDM = non insulin dependent diabetes.

- **Type A insulin resistance** describes a group of patients with severe insulin resistance. It was originally described in women presenting with hirsutism and oligomenorrhea, but it is also found in men who remain asymptomatic until they develop impaired glucose tolerance.

- **Pseudoacromegaly**, so termed because these subjects, who have severe insulin resistance, have soft tissue and muscle enlargement similar to that seen in acromegaly.

- **Partial lipodystrophy**, another severe form of insulin resistance in which subjects have partial lipoatrophy and may have lipohypertrophy, muscle enlargement, hyperlipidemia and fatty liver. This has recently been shown to result from a mutation in the gene encoding lamin A/C.

Professor Hattersley can be contacted for further information about diagnostic genetic testing in MODY, which is offered at the Royal Devon and Exeter Hospital.

References

1. O'Rahilly S, Spivay RS, Holman RR, Nugent Z, et al. Type II diabetes of early onset: a distinct clinical and genetic syndrome? Br Med J 1987;294:923–8.
2. Zimmet P, Turner R, McCarty D, Rowley M, et al. Crucial points at diagnosis. Type 2 diabetes or slow type 1 diabetes. Diabetes Care 1999;22(Suppl 2):S59–64.
3. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, et al. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with non-insulin-dependent onset of disease. Diabetes 1993;42:358–62.
4. Groop LC, Bottazzo GF, Doniach D, Islet cell antibodies identify latent type 1 diabetes in patients aged 35–75 at diagnosis. Diabetes 1986;35:237–41.
5. Tattersall RB. Mild familial diabetes with dominant inheritance. Q J Med 1974;43:339–57.
6. Hattersley AT. Maturity-onset diabetes of the young: clinical heterogeneity explained by genetic heterogeneity. Diabet Med 1998;15:15–24.
7. Maassen JA, Kadowaki T. Maternally inherited diabetes and deafness: a new diabetes subtype. Diabetologia 1996;39:375–82.
8. Inoue H, Tanizawa Y, Wassen J, Behn P, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet 1998;20:143–8.
9. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 1995;346:1458–63.
10. Beales PL, Elcloglu N, Woolf AS, Parker D, et al. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet 1999;36:437–46.
11. Holm VA, Cassidy SB, Butler MG, Hanchett JM, et al. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics 1993;91:398–402.
12. American Society of Human Genetics/ American College of Medical Genetics and Technology Transfer Committee: diagnostic testing for Prader-Willi and Angelman syndromes. Am J Hum Genet 1986;58:1085–8.
13. Marshall JD, Ludman MD, Shea SE, Salisbury SR, et al. Genealogy, natural history and phenotype of Alstrom syndrome in a large Arcadian kindred and three additional families. Am J Med Genet 1997;73:150–61.
14. O'Rahilly S, Moller DE. Mutant insulin receptors in syndromes of insulin resistance. Clin Endocrinol 1992;36:121–32.

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Further Information

The most up-to-date information on specific genetic disorders is found on the Online Mendelian Inheritance in Man (OMIM) database at: http://www.ncbi.nlm.nih.gov/omim/ or http://www.ncbi.nlm.nih.gov/omim/