GUIDELINES FOR ESTABLISHING THE AETIOLOGY OF DIABETES IN YOUNG ADULTS

With the increasing tendency for Type 2 DM to present in young adults and the recent expansion in knowledge about monogenic causes of diabetes, establishing the aetiology of diabetes in young adults is not necessarily straightforward. The differential diagnosis includes:

1. Type 1 Diabetes
Type 1 DM can occur at any age and is typically associated with a relatively short prodrome of weight loss and with ketonuria/ketonaemia at presentation.

2. Latent Autoimmune Diabetes of Adults (LADA)
The presentation is more insidious than that of Type 1 DM; patients are often erroneously diagnosed as having ‘non-obese’ Type 2 DM and are commenced on oral hypoglycaemic agents. Conversion to insulin is usually required within a matter of months, but may take up to 10 years. These patients often have GAD antibodies and have low fasting and post-glucagon-stimulated c-peptide.

3. Maturity Onset Diabetes of the Young (MODY)
This form of diabetes is inherited in an autosomal dominant manner. There are now five subtypes, but the commonest are MODY 3 and MODY 2. MODY 3 is associated with a mutation in the HNF1α gene and may present at any age. Microvascular complications readily occur, but affected individuals appear to be very sensitive to sulphonylurea therapy. By contrast, MODY 2 is associated with mild hyperglycaemia and no significant risk of microvascular complications. The genetic defect is in the glucokinase gene and it may present, in women, as ‘gestational diabetes’.

4. Type 2 Diabetes
Type 2 DM is associated with insulin resistance and central abdominal obesity. It is highly prevalent in certain ethnic groups, especially Asians. In such groups, it is recognised that individuals are much more insulin resistant for a given BMI than
Caucasians. Thus, for example, an Asian with a BMI of 23 will generally be as insulin resistant as a Caucasian with a BMI of 25. Affected individuals generally exhibit one or more features of the metabolic syndrome e.g. hypertension; low HDL cholesterol; high fasting triglycerides.

5. **Mitochondrial Diabetes**
This form of diabetes is maternally inherited and is associated with sensori-neural deafness. It is especially prevalent in Japanese people.

6. **Secondary Diabetes**
The commonest cause is probably drug therapy, notably exogenous glucocorticoids. Other causes include pancreatic insufficiency (including pancreatic carcinoma and cystic fibrosis), haemochromatosis, Cushing’s syndrome, acromegaly and phaeochromocytoma.

7. **Rare Causes of Insulin Resistance**
These include disorders such as lipoatrophy and other lipodystrophies, which are usually readily identifiable on clinical examination.

**Importance of Making the Correct Diagnosis**
Making the correct diagnosis of the aetiology of diabetes in a young adult is important because it allows therapy to be appropriately tailored to the individual. Thus, for example, people with MODY 2 (and their insurers) need be reassured that they have ‘mild’ diabetes, which is unlikely to require specific therapy unless pregnancy occurs. People with MODY can be often managed with sulphonylurea agents, while patients with LADA will probably require early insulin therapy. The diagnosis of MODY or mitochondrial diabetes also permits family members to be screened, so that carriers can be monitored for the development of diabetes and non-carriers reassured.
Importance of Clinical Variables in Establishing the Aetiology of Diabetes

The clinical features of Type 1 diabetes and of the rarer secondary causes should be familiar to all doctors performing diabetes clinics. The main diagnostic difficult is usually between Type 2 DM, LADA and MODY.

*Family history is not a good discriminator of Type 2 DM and MODY.* Although MODY is inherited in an autosomal dominant manner, but the penetrance is not 100% i.e. not all carriers will develop diabetes. Moreover, the diagnosis of diabetes may not have been made in preceding generations. Thus, only two thirds of people with MODY will report diabetes in a parent. In addition, the genetic element of Type 2 DM is well recognised, and it also appears that a younger age of onset of Type 2 DM is accompanied by an increasing prevalence of parental Type 2 DM, i.e. if an individual has one or more parents with Type 2 DM, they are likely to develop Type 2 DM at a younger age than someone with no parental history.

The best discriminators of Type 2 DM and MODY are *hypertension, low HDL cholesterol, high fasting triglycerides* and *high BMI* – each of which make Type 2 DM more likely. MODY has not, as yet, been identified in any Asian populations.

The algorithm at the end of this protocol gives guidelines about the steps that should be followed in the investigation of someone with new-onset diabetes. **It is not an absolute guideline**, i.e. common sense must still be employed. Thus, for example, someone with a BMI >25 or of Asian extraction could have Type 1 diabetes, or indeed any other form of the disease.

**Screening for Monogenic Diabetes**

If you suspect monogenic diabetes (MODY or mitochondrial diabetes), genetic testing is available via the clinical genetics laboratory. An EDTA sample of blood is required. Genetic testing is best arranged through Jill Little, our MODY Link nurse. Jill can take a family history and ensure that the relevant genetic tests are requested.
Screening for GAD Antibodies

Screening for GAD antibodies can be arranged through Susan Walker in Clinical Biochemistry.

Algorithm for Investigating Young People with New-Onset Diabetes

Diabetes
Age 20-45
No features of secondary diabetes or lipodystrophy

- Type 1 diabetes

  Ketonuria/ketonaemia and/or significant weight loss

- Type 2 diabetes

  Asian origin
  BMI >25
  Hypertension
  Low HDL cholesterol
  High triglycerides

- ? Mitochondrial Diabetes
  – send blood to Clinical Genetics

- Maternal Inheritance
  Sensori-neural deafness

- MODY Mutation
  Send blood, via Clinical Genetics to Exeter for MODY screen

- Normal

- Send blood to Bristol for GAD status

- LADA

- Discuss with Consultant