Definition
Monogenic diabetes results from the inheritance of a mutation or mutations in a single gene. It may be dominantly or recessively inherited or may be a \textit{de novo} mutation and hence a spontaneous case. In children, almost all monogenic diabetes results from mutations in genes that regulate beta-cell function although diabetes can rarely occur from mutations resulting in very severe insulin resistance (C). \cite{1}.

Diagnosis
Why diagnose monogenic diabetes?
The majority of patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as Type 1 or Type 2 diabetes \cite{2} (C). It is important to correctly diagnose monogenic diabetes as it can predict the clinical course of the patient, explain other associated clinical features and most importantly guide the most appropriate treatment. In addition, making a diagnosis will have implications for other family members often correcting the diagnosis and treatment for other diabetic family members as well as allowing appropriate genetic counseling.

Clinical presentation of monogenic diabetes
Clinical presentations in children when a diagnosis of monogenic diabetes should be considered and are discussed below include:

1. Neonatal diabetes and diabetes diagnosed within the first 6 months of life.
2. Familial diabetes with an affected parent
3. Mild (5.5–8.5 mmol/l) fasting hyperglycaemia especially if young or familial
4. Diabetes associated with extra pancreatic features

When to suspect a diagnosis of Type 1 diabetes in children may not be correct?
Features in children initially thought to have Type 1 diabetes that should suggest a possible diagnosis of monogenic diabetes are shown below. None of these...
are absolute and should be considered as together rather than in isolation (C) (3).

i) A diagnosis of diabetes before 6 months (B) (in Type 1: <1% (4))

ii) Family history of diabetes with a parent affected (C) (in Type 1: 2–4% (5))

iii) Evidence of endogenous insulin production outside the ‘honeymoon’ phase (after 3 years of diabetes) with detectable C peptide (> 200 nmol/l) when glucose > 8 mmol/l (E) (in Type 1 DM: 1–5%).

iv) When pancreatic islet autoantibodies are absent, especially if measured at diagnosis (C) (in Type 1: 3–30% (6–8)). The great variation in antibody prevalence in series probably represents differences in assays and means it is hard to apply published series directly into clinical practice. Absent antibodies should lead to other investigation/consideration rather than leading directly to genetic tests (E).

When to suspect a diagnosis of Type 2 diabetes in children may not be correct?

Features in children initially thought to have Type 2 diabetes that should suggest a possible diagnosis of monogenic diabetes are shown below. Note most Type 2 diabetes in youth will meet former classification for MODY (diagnosed < 25, autosomal dominant inheritance and non-insulin dependent (C) (9–12)).

i) Not markedly obese or diabetic family members who are normal weight (in Type 2: 20% (12))

ii) Acanthosis nigricans not detected (in Type 2: 10% (9))

iii) Ethnic background has a low prevalence of Type 2 diabetes race e.g. European Caucasian (in Type 2: 0–45%)

iv) No evidence of insulin resistance with fasting C peptide within the normal range (in Type 2: 0-20% (9–12))

Making a diagnosis of monogenic diabetes

As well as having clinical features that are unusual for Type 1 and Type 2 diabetes a patient in whom a diagnosis of monogenic diabetes should also have the features of a specific genetic subtype of monogenic diabetes (E). The features of the commoner monogenic diabetes are given below.

While in Type 1 and Type 2 diabetes there is no single diagnostic test, this is not the case in monogenic diabetes where in > 80% of cases a molecular genetic diagnosis can be made by DNA testing (C). Molecular genetic testing is offered in most European countries and the USA but many labs will test patients from other countries (for example www.diabetesgenes.org and www.mody.no). These tests are expensive (up to €500/$600) but can have a big impact on management of the proband and other family members who will be cheaper as the mutation is known (€100/$120). Some recently described monogenic diabetes genes like Kir6.2 testing in patients diagnosed less than 6 months may be available as research tests for no charge (see www.diabetesgenes.org). Approval from the patient’s insurance company should be sought prior to sending DNA when applicable.

Given the limited resources available it is vital that these tests are used in situations where they are likely to be positive and will alter clinical care. This will involve careful clinical selection and performing physiological tests like C peptide and autoantibody measurement as well as testing other family members before doing molecular genetic tests (E).

Specific subtypes of monogenic diabetes and their management

Neonatal diabetes and diabetes diagnosed within the first 6 months of life. There is good evidence that diabetes diagnosed in the first 6 months is not Type 1 diabetes as autoantibodies are rare and HLA genotyping is actually protective for Type 1 in these patients (B) (4). Neonatal diabetes is another area which has rapidly moved from a clinical to a molecular genetic classification (13, 14). Neonatal diabetes is insulin requiring diabetes which is usually diagnosed in the first three months of life. Clinically two subgroups were recognised: transient neonatal diabetes mellitus (TNDM) that resolved at a median of 12 weeks and then did not require any treatment although as many as 50% of cases would ultimately relapse (B) (15, 16); in contrast permanent neonatal diabetes mellitus (PNDM) required continual treatment from diagnosis. For most patients with both types of neonatal diabetes the molecular aetiology can now be defined. The majority of patients with TNDM have an abnormality of imprinting of the ZAC and HYMAI genes on chromosome 6q (B) (14, 15) while the commonest known cause of PNDM are mutations in the KCNJ11 gene encoding the Kir6.2 subunit of the beta-cell KATP channel (B) (17, 18). If both parents are glucose intolerant, homozygous or compound heterozygous mutations in glucokinase are most frequent (19, 20).

Differential diagnosis

When diabetes is diagnosed in the neonatal period it is difficult to tell if it is likely to be transient or permanent although the features in Table 1 can help differentiate the possible different subtypes and can be used to guide molecular genetic testing.
Table 1. Characteristics of diabetes presenting in the first 6 months of life (modified from reference (13))

<table>
<thead>
<tr>
<th>Gene clinical syndrome inheritance</th>
<th>Type of diabetes</th>
<th>% in Consanguineous or isolated populations</th>
<th>Median birth weight (SDS)</th>
<th>Median (range)</th>
<th>Pancreatic appearance</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZAC/HYAMI imprinting defect on 6q24</td>
<td>TNDM</td>
<td>rare</td>
<td>2,100 g (2.94)</td>
<td>0.5 (0–4)</td>
<td>Normal</td>
<td>Macroglossia (23%)</td>
</tr>
<tr>
<td>Kir6.2 (KCNJ11)</td>
<td>PNDM</td>
<td>rare</td>
<td>2,580 g (1.73)</td>
<td>6(0–260)</td>
<td>Normal</td>
<td>Developmental delay (20%) Epilepsy (6%) DKA (30%)</td>
</tr>
<tr>
<td>SUR1 (ABCC8)</td>
<td>PNDM TNDM</td>
<td>rare (10%)</td>
<td>2600 g (1.7)</td>
<td>6 (0–17)</td>
<td>Normal</td>
<td>Developmental delay Epiphyseal dysplasia (90%) Osteopenia (50%), acute liver failure (75%), developmental delay (80%), hypothyroidism (25%)</td>
</tr>
<tr>
<td>EIF2AK3 Wolcott-Rallison syndrome recessive</td>
<td>PNDM TNDM (78%)</td>
<td>rare</td>
<td>3000 g (1.0)</td>
<td>13 (6–65)</td>
<td>Atrophy of pancreas (?) Exocrine dysfunction (25%)</td>
<td></td>
</tr>
<tr>
<td>INS</td>
<td>PNDM</td>
<td>Rare</td>
<td>2600 g (1.7)</td>
<td>9(0–26)</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>FOXP3</td>
<td>PNDM</td>
<td>Rare</td>
<td>2860 g (1.2)</td>
<td>6(0–30)</td>
<td>?</td>
<td>Only boys affected Chronic diarrhoea with villous atrophy (95%); Pancreatic and thyroid autoantibodies (75%); Thyroiditis (20%), eczema (50%); anaemia (30%); often die young (1st yr)</td>
</tr>
<tr>
<td>IPEX syndrome X linked</td>
<td>PNDM</td>
<td>Rare</td>
<td>1720 g (2.75)</td>
<td>Normal</td>
<td></td>
<td>Parents have fasting hyperglycaemia as heterozygotes</td>
</tr>
<tr>
<td>GCK (glucokinase)</td>
<td>PNDM</td>
<td>85%</td>
<td>1720 g (2.75)</td>
<td>Normal</td>
<td></td>
<td>Parents may have early-onset diabetes as heterozygotes</td>
</tr>
<tr>
<td>IFP1 recessive</td>
<td>PNDM</td>
<td>50%</td>
<td>2140 g (2.97)</td>
<td>Absent</td>
<td></td>
<td>Renal developmental disorders</td>
</tr>
<tr>
<td>HNF-1β dominant (60%) spontaneous</td>
<td>TNDM</td>
<td>2 Rare</td>
<td>1900 g (3.21)</td>
<td>Atrophy</td>
<td></td>
<td>Severe neurological dysfunction and cerebellar hypoplasia</td>
</tr>
<tr>
<td>PTF1A recessive</td>
<td>PNDM</td>
<td>100%</td>
<td>1390 g (3.8)</td>
<td>Atrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Transient neonatal diabetes from imprinting anomalies on 6q24

Imprinted anomalies of the 6q24 locus involving the ZAC and HYAMI genes are the most common cause of neonatal diabetes and result in TNDM (B) (14, 15, 21). The commonest 6q24 anomalies are inherited paternal duplications or paternal uniparental disomy although methylation anomalies are being more frequently identified (E) (16). Diabetes associated with this is typically diagnosed within the first week and resolves around 12 weeks (B) (15). In approximately 50% of cases diabetes will reoccur during the pediatric age range (B) (15). Apart from macroglossia seen in 23% there are no non-pancreatic features (B) (15).

Initial glucose values can be very high (range 12-57 mmol/l) and so insulin is used initially although the dose can rapidly be reduced. Once patients have relapsed patients should remain under annual follow up due to the risk of diabetes relapsing. On relapse patients are not insulin dependent and can be treated with diet initially although subsequently often need insulin (E) (14). The response to oral treatment such as sulphfonylureas or metformin is uncertain.

Permanent neonatal diabetes, transient neonatal diabetes and diabetes diagnosed in the first 6 months of life due to mutations in the ATP-sensitive potassium channel

Glucose-stimulated insulin secretion requires closure of the ATP-sensitive potassium channel of the beta cell. This channel consists of four potassium channel (Kir6.2) subunits and four sulfonylurea receptor subunits. Activation mutations of the genes encoding these subunits keep the channels open, preventing insulin secretion and thus they cause neonatal diabetes. Kir6.2 mutations are the second commonest cause of mutations in patients with diabetes diagnosed in the first 6 months of life (B) (17, 18). While some (10%) have a remitting form of diabetes that may latter relapse the majority have permanent neonatal diabetes (C) (22). Most patients have isolated diabetes although neurological features are seen in 20% of patients. Despite being a heterozygous mutation most have no family history as 90% of cases are spontaneous mutations. The most severe defect is very marked developmental delay of motor and social function and generalised epilepsy often with hypersarrhythmia as seen in West syndrome (C) (17). This has been called developmental delay, epilepsy and neonatal diabetes (DEND) syndrome (18). More common is the intermediate DEND syndrome where patients have less severe developmental delay and do not have epilepsy (18).

Patients with Kir6.2 mutations have all the clinical features of insulin dependency as 30% present with ketoacidosis and they usually do not have detectable C peptide and so were treated with insulin (C) (18). It has recently been shown that these patients can not only be successfully treated with oral sulphonylureas but can also get better glycaemic control without an increase in hypoglycaemia. The doses needed are high when calculated on a per kg body weight basis compared to adults with patients typically needing 0.5 mg/kg/glibenclamide/day although some may need as much as 1 mg/kg/day (C) (23–29). With time many patients have been able to reduce their doses of sulphfonylureas but maintain excellent glycemic control (E).

SUR1 mutations cause 12% of neonatal diabetes, and often cause transient diabetes (30, 31).

Wolcott–Rallison syndrome

Wolcott–Rallison syndrome is a rare autosomal recessive condition characterised by early onset diabetes, epiphyseal dysplasia, renal impairment, acute hepatic failure, and developmental delay (B) (32, 33). It is associated with mutations in EIF2AK3 (34). Diabetes usually presents in infancy, but may be latter, and is associated with ß cell loss, leading to insulin deficiency without autoimmune pathology. Insulin treatment is required. Wolcott–Rallison syndrome should be considered in any patient with diabetes in the first 3 years who has epiphyseal dysplasia or acute severe hepatic failure (C, E) (32).

Other causes of neonatal diabetes

In Table 1 the clinical features of other causes of neonatal diabetes are outlined. The most common other causes are INS mutations that do not have extra-pancreatic features (35). Scanning the pancreas to assess if it is present and its size, checking for exocrine pancreatic function and pancreatic autoantibodies (found in IPEX syndrome) are the most useful diagnostic tests before proceeding to molecular genetic testing (E). All other causes need to be treated with insulin. Some pediatricians consider these patients are easiest managed on subcutaneous insulin pumps. In patients with pancreatic aplasia exocrine pancreatic supplements will be required.

Familial diabetes

The commonest causes of familial diabetes or familial hyperglycaemia are shown in Table 2 below:
Table 2. Characteristics of common forms of monogenic diabetes and hyperglycemia

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Number of families identified in UK</th>
<th>Typical age of presentation in paediatric clinic (range)</th>
<th>Typical glucose presentation (range) mmol/l</th>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-1α (MODY3)</td>
<td>Dominant</td>
<td>197</td>
<td>14 (4–18)</td>
<td>17 (11–26) Large increment in an OGTT (2hr -0hr usually &gt; 5 mmol/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low renal threshold</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Progressive hyperglycaemia with age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensitive to sulphonylureas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Similar to HNF-1α but renal threshold normal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Macrosomia very common and 20% have prolonged neonatal hypoglycaemia</td>
</tr>
<tr>
<td>HNF-4α (MODY1)</td>
<td>Dominant</td>
<td>22</td>
<td>17 (5–18)</td>
<td>15 (9–20) Usually incidental finding at diagnosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting glucose in range 5.5–8 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Small increment in an OGTT (2hr -0hr usually &lt; 3.5 mmol/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Little deterioration in glycaemia with age</td>
</tr>
<tr>
<td>Glucokinase</td>
<td>Dominant (may not be diagnosed in parents as mild)</td>
<td>152</td>
<td>10 (0–18)</td>
<td>11 (5.5–16) Usually incidental finding at diagnosis.</td>
</tr>
<tr>
<td>(MODY2)</td>
<td></td>
<td></td>
<td></td>
<td>Fasting glucose in range 5.5–8 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Small increment in an OGTT (2hr -0hr usually &lt; 3.5 mmol/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Little deterioration in glycaemia with age</td>
</tr>
</tbody>
</table>

Children and young adults with diabetes and a strong family history of diabetes: hepatocyte nuclear factor 1 alpha (HNF-1α) gene mutations (MODY3)

The possibility of monogenic diabetes should be considered when ever a parent has diabetes even if they are thought to have Type 1 or Type 2 diabetes (E). The most common form of monogenic diabetes which results in familial diabetes (known in the past as maturity-onset diabetes of the young (MODY)) are HNF-1α mutations (B) (36). The clinical characteristics of patients with HNF-1α mutations are:

i) Young-onset diabetes that shows characteristics of not being insulin-dependent e.g. not developing ketoacidosis in the absence of insulin, good glycaemic control on a small dose of insulin, or detectable C-peptide measured when on insulin with glucose > 8 mmol/l outside a normally expected honeymoon period (3 years) (E).

ii) Family history of diabetes. This may be insulin treated and considered to be “type 1” diabetes. This would typically be diagnosed in the 20s, 30s or 40s. There may also be an affected grandparent although often these are diagnosed after 45 yrs (C).

iii) Oral glucose tolerance tests in early stages tend to show a very large glucose increment usually > 5 mmol/l (33). Some subjects may have a normal fasting value but still rise into the diabetic range at 2 hrs (33) (B).

iv) Glycosuria at relatively normal blood glucose levels are often seen as these patients have a low renal threshold (B) (33).

v) Marked sensitivity to sulphonylureas resulting in hypoglycaemia despite poor glycaemic control before starting sulphonylureas (C) (34, 36).

Treatment

Patients with HNF-1α gene mutations can initially be treated with diet although they will have marked post prandial hyperglycaemia high carbohydrate food as the beta-cell defect results in insufficient increase in insulin secretion with hyperglycaemia (37).

Most patients will need pharmacological treatment as they show progressive deterioration in glycaemic control throughout life and are at risk of considerable micro-vascular and macro-vascular complications (B, C) (38).

The first treatment to be used in children who are not controlled on insulin should be low dose sulphonylureas which results in a 4 fold greater lowering of glucose than metformin (A) (39). These patients are extremely sensitive to sulphonylureas and as long as they do not have problems with hypoglycaemia can be maintained on these for many decades (C) (34). Glycaemic control in sulphonylureas is often better than that achieved on insulin especially in children and young adults (40). The dose of sulphonylureas should initially be low (1/4 of the normal starting dose in adults) to avoid hypoglycaemia (E). If there is hypoglycaemia despite dose titration of a once or twice daily sulphonylurea preparation such as Gliclazide a slow release preparation or meal time doses with a short acting agents like nateglinide may be considered (C) (4).
Children and young adults with diabetes and a strong family history of diabetes: hepatocyte nuclear factor 4 alpha (HNF-4α) gene mutations (MODY1)

Diabetes due to mutations of the HNF-4α gene are considerably less common (Table 2) than diabetes due to mutations of the HNF-1α gene but has similar characteristics except there is not a low renal threshold and the age of diagnosis may be later (C) (45). HNF-4α mutations should be considered when HNF-1α sequencing is negative but the clinical features were strongly suggestive of HNF-1α (45). Patients are often sensitive to sulphonylureas (C) (46).

Other causes of familial diabetes

A handful of families with autosomal dominant non-insulin dependent diabetes have been described with mutations in IPF1 (MODY4) (47), NeuroD1 (MODY6) (48, 49) and recently the carboxyl ester lipase (CEL) gene (MODY7) (50) but these are so unusual they do not need to be tested for in children with diabetes except in a research setting (E) or when there are additional phenotypes such as pancreatic exocrine dysfunction (50).

Mild fasting hyperglycemia: due to glucokinase mutations (MODY2)

The finding of raised fasting blood glucose in the range of 5.5–8.5 mmol/l is unusual in children and young adults. This always raises concern that they may be about to develop type 1 diabetes or the patient has Type 2 diabetes. However a considerable proportion of these patients with persistent mild fasting hyperglycaemia will have a heterozygous mutation in the glucokinase gene. The phenotype associated with glucokinase mutations is remarkably similar for all mutations. The following features suggest a diagnosis of a glucokinase mutation:-

i) The fasting hyperglycaemia is persistent and stable over a period of months or years (37)

ii) HbA1c is typically just below or just above the upper limit of normal (5.5–5.7%)

iii) In an oral glucose tolerance test the increment (2hr glucose—fasting glucose) is small (typically < 3.5 mmol/l) although because of the variability of the oral glucose tolerance test this should not be considered an absolute criteria (37).

iv) Parents may have “type 2 diabetes” or may not be diabetic. On testing one parent will have a mildly raised fasting blood glucose, in the range of 5.5–8.5 mmol/l, as this is an autosomal dominant condition (C) (37). Testing of apparently unaffected parents fasting glucose is important when considering a diagnosis of a glucokinase mutation (E).

Treatment

The fasting hyperglycaemia does not deteriorate significantly and the glucose is regulated at the higher set point (37). This is rarely associated with any microvascular or macrovascular complications even when no treatment is given throughout life (C) (51).

An important point is that these patients do not need treating in the paediatric age range. There is very little if any response to either oral hypoglycemic agents or insulin (E). Exogenous insulin results in reduction of endogenous insulin secretion and so the degree of glycaemia will be maintained, explaining why these children can be treated with insulin without significant hypoglycemia.

Genetic syndromes associated with diabetes

When diabetes in a child is associated with other multi-system disease the possibility of a monogenic syndrome that explains all features should be considered.

The Online Mendelian inheritance in Man (OMIM) website (access through the NCBI website http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) can help with clinical features and to know if the gene has been defined and hence molecular genetic testing is available. For described and previously undescribed syndromes help can be obtained through the ISPAD rare diabetes collection (contact through link on the ISPAD web page or through www.diabetesgenes.org). The most common genetic syndromes which include diabetes are listed below:

Diabetes insipidus, diabetes mellitus, optic atrophy, deafness (DIDMOAD) syndrome (Wolfram syndrome)

Wolfram syndrome is an autosomal recessive syndrome in which the association of diabetes with progressive optic atrophy under 16 years of age is diagnostic (52). The syndrome is more common in races where consanguineous marriages are frequent. Other features are bilateral sensorineural deafness, diabetes insipidus, dilated renal tracts, and truncal ataxia or more protean neurological signs, with the complete phenotype seen in 75% of patients with increasing prevalence with age. The order of appearance of the neurological symptoms may vary even within families. The median age of death in Wolfram syndrome is 30 years (52). Mutations in the gene for Wolfram syndrome (WFS1)
are present in at least 90% of patients with clinical Wolfram syndrome (53–55).

The diabetes is non-autoimmune and insulin deficient and presents at a mean age of six years (52). Patients require insulin treatment from the time of diagnosis but autoantibodies are not present (C) (52).

Thiamine responsive megaloblastic anemia (Roger’s syndrome)

Thiamine responsive megaloblastic anemia (TRMA) is a rare recessive, genetic syndrome of early onset megaloblastic anemia (which responds to thiamine) is associated with diabetes and sensorineural deafness. This results from mutations in the gene SLC19A2 (56). The diabetes, which is insulin deficient in nature, is responsive to thiamine in some patients, although all seem to develop an insulin requirement in the long term (C) (57). Deafness is unresponsive to thiamine.

Renal cysts and diabetes syndrome due to a Hepatic Nuclear Factor 1-β mutation

Although initially described as a subgroup of familial diabetes (MODY5) it is now clear that patients with mutations in HNF-1β rarely present with isolated diabetes (58). Renal developmental disorders especially renal cysts and renal dysplasia are present in almost all patients with mutations or gene deletions (59), may be diagnosed in utero and precede the diagnosis of diabetes (B). Other features which may be present in children include uterine and genitalia developmental anomalies, hyperuricaemia, gout and abnormal liver function tests (58) A diagnosis of HNF-1β should be considered in any child with diabetes who also has non-diabetic renal disease.

Patients with HNF-1β mutations, unlike patients with HNF-1α mutations, are not sensitive to sulphonylureas and so usually require insulin treatment (60). Pancreatic size is reduced reflecting a reduction in both the endocrine and exocrine pancreas and sub-clinical exocrine deficiency is present in most patients (61) but it is uncertain if this should be treated if it is asymptomatic.

Mitochondrial diabetes

Maternal transmission of mutated or deleted mitochondrial DNA (mtDNA) can result in maternally inherited diabetes although they are not usually in the paediatric age range. Although several mutations and deletions have been implicated, the strongest evidence relates to a point substitution at nucleotide position 3243 (A to G) in the mitochondrial tRNA (leu(UUR)) gene (B) (62). An identical mutation occurs in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome); and there may be some overlap between these syndromes in family members. Mitochondrial diabetes is commonly associated with sensorineural deafness and short stature. The diabetes is characterized by progressive non-autoimmune beta-cell failure and may progress to needing insulin treatment rapidly.

Insulin resistance syndromes: Type a insulin resistance, leprechaunism, Rabson-Mendenhall syndrome and lipodystrophy

The key feature of all insulin resistance syndromes are acanthosis nigricans, androgen excess and massively

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>Clinical features</th>
<th>Acanthosis Nigri cans</th>
<th>Androgen Excess &amp; Hypertrichosis</th>
<th>Insulin levels</th>
<th>Gene involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leprechaunism</td>
<td>Congenital</td>
<td>Abnormal facies. Large genitalia. SGA and growth retardation</td>
<td>Yes—marked</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>Rabson-Mendenhall</td>
<td>Congenital</td>
<td>Rarely survive infancy Extreme growth retardation Abnormal dentition IR in absence of obesity</td>
<td>Yes—marked</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>Type A</td>
<td>Adolescence</td>
<td>Abnormal facies. Large genitalia. SGA and growth retardation</td>
<td>Yes—marked</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>Congenital or Adolescence</td>
<td>Loss of subcutaneous fat—partial or total</td>
<td>Yes—marked</td>
<td>↑↑</td>
<td>PCO</td>
<td>Seipin &amp; AGPAT2 (recessive) Lamin AC &amp; PPARG (dominant)</td>
</tr>
</tbody>
</table>

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raised insulin concentrations in the absence of obesity (1). The more severe the insulin resistance and the earlier the onset the more likely is diabetes (C) (1). A summary of some of the key clinical features is shown below (adapted from Musso et al. (1)).

Treatment of severe insulin resistance is very difficult and most patients with diabetes have poor glycaemic control and frequently develop long term complications (C) (1). Approaches used include the use of the insulin sensitisers metformin and glitazones but their impact is limited when the insulin resistance is very severe. Insulin is the mainstay of treatment and U500 insulin and insulin pumps are usually required (1). In partial lipodystrophy Metformin may have benefit and insulin is not required in the early stages (C) (63). In total lipodystrophy the response of diabetes to recombinant insulin is limited when the insulin resistance is very severe.

Recommendations

Advances in molecular genetics have led to the identification of the genes associated with many clinically identified subgroups of diabetes. The identification of genes has explained clinical heterogeneity in conditions defined on the basis of when they were diagnosed e.g. neonatal diabetes and MODY. Now molecular genetics is being used as a diagnostic test which can help define the diagnosis and treatment of children with diabetes. As these tests are expensive genetic testing should be limited to those who on clinical grounds are likely to be positive. E

References

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