

Acquired non-type 1 diabetes in childhood: subtypes, diagnosis, and management

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Over the past 30 years it has become apparent that not all diabetes presenting in childhood is autoimmune type 1. Increasingly type 2 diabetes, maturity onset diabetes of the young, iatrogenic diabetes, and rare syndromic forms of diabetes such as Wolfram's syndrome have been identified in children. This review is aimed at the general paediatrician looking after children with diabetes, and aims to provide an algorithm for assessment, investigation, and suggested management for the newly diagnosed child with suspected non-type 1 diabetes. This article will also be relevant to the child with atypical diabetes—that is, on low insulin doses outside the honeymoon period.

Diabetes is the third most common chronic disease of childhood.¹ Type 1, or autoimmune diabetes accounts for about 99% of cases. Type 1 diabetes is characterised by β cell destruction, an autoimmune pathological process, and absolute insulin requirement.² Over the past 30 years it has been recognised that not all diabetes in childhood is type 1. Diabetes syndromes such as neonatal diabetes³ and Wolfram syndrome have been described;⁴ genetic forms of diabetes such as maturity onset diabetes of the young have been defined;⁵ and more recently both iatrogenic and type 2 diabetes have been noted in childhood.^{6,7} These subtypes of diabetes are rare; in 2000 a UK national survey of clinicians looking after children with diabetes found only 0.7% of children with diabetes had non-type 1 diabetes, although this is likely to be an underestimate (table 1).⁸ These patients are important because they cause diagnostic uncertainty and often need different management. This review will discuss non-type 1 diabetes in childhood, and suggest a flow chart for diagnosis and treatment. Neonatal diabetes is a specialist management problem and beyond the scope of this article.

DIAGNOSTIC SUBGROUPS

Diabetes may present symptomatically or be an incidental finding. The World Health Organisation has laid down criteria for diagnosis of diabetes: a venous plasma glucose ≥ 7 mmol/l fasted or ≥ 11.1 mmol/l unfasted on more than one occasion.² Diabetes in an asymptomatic child should never be diagnosed on a single test of plasma glucose, but a single measurement in excess of the established values in a child with symptoms of polyuria, polydipsia, and weight loss is sufficient for diagnosis.²

This review considers children at diagnosis in three categories: those that are unwell or have ketonuria, those that are well with mild or absent symptoms, and those that have features of other chronic disorders or factors predisposing to diabetes (diabetes and disorder). These three groups are outlined in fig 1.

THE UNWELL OR KETOTIC CHILD WITH NEWLY DIAGNOSED DIABETES (FIG 1, BOX A)

The unwell or ketotic child must be assumed to have type 1 diabetes unless there is good evidence otherwise. Ketonuria is present only in a minority of patients presenting with type 2 diabetes.⁹ Obesity is suggestive of type 2 diabetes, but some children with type 1 diabetes are also obese at presentation. This reflects the increasing prevalence of obesity in the general population rather than a change in the pathophysiology of type 1 diabetes.¹⁰ We recommend that unwell or ketotic children be insulin treated at presentation. The diagnosis and management can then be reviewed subsequently if there are atypical features to the diabetes. Features such as low insulin requirement outside the honeymoon period (that is, <0.5 units/kg >3 years after diagnosis),¹¹ no subsequent ketonuria at times of illness, strong family history of non-type 1 diabetes, and development of auditory, ophthalmic, or renal abnormalities, should prompt consideration of other diabetes subtypes. Measurement of pancreatic antibody levels is useful in these cases. The common antibodies tested for in diabetes are those to glutamic acid decarboxylase-65 (GAD-65), tyrosine phosphatase (IA-2 α), and the islet cell (ICA). Antibodies to IA-2 α are present in 68.2–79%, GAD-65 in 25–76%, and ICA in 80.5–89.9% of paediatric white type 1 patients at diagnosis,^{12,13} although absence of antibodies does not exclude type 1 diabetes. African-Americans and Asian-Indians with type 1 diabetes seem to have a lower prevalence of GAD-65 antibodies,^{14,15} and there are low antibody levels in normal populations.¹⁶ We recommend measuring GAD-65 antibodies to confirm autoimmune diabetes in children where there is diagnostic doubt.

Abbreviations: CFRD, cystic fibrosis related diabetes; GAD-65, glutamic acid decarboxylase-65; HNF-1 α , hepatocyte nuclear factor 1 α ; MODY, maturity onset diabetes of the young; OMIM, Online Mendelian Inheritance in Man (database); PCOS, polycystic ovarian syndrome; TRMA, thiamine responsive megaloblastic anaemia

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Table 1 Findings of the 2000 UK national survey of diabetes in childhood⁸

Type of diabetes	No. patients	%
Type 1	15143	99
Type 2	24	0.16
MODY	17	0.11
Cystic fibrosis	8	0.05
Prader-Willi	4	0.03
Wolfram	5	0.03
Isletogenic	6	0.04
Neonatal diabetes	3	0.02
Pancreatectomy	3	0.02
Down's	2	0.01
Others/unclassified	40	0.26

THE WELL CHILD WITH NEWLY DIAGNOSED DIABETES (FIG 1, BOX B)

A well child with hyperglycaemia is likely to have one of four diagnoses: type 1 diabetes (although it is rare to have children with type 1 diabetes present with hyperglycaemia and total lack of ketones); type 2 diabetes; maturity onset diabetes of the young (MODY); or autoimmune diabetes with slow onset.

Type 2 diabetes

Type 2 diabetes is characterised by insulin resistance and defective insulin secretion.² Incidence figures for type 2

diabetes vary widely worldwide.¹⁷ We propose that when making a diagnosis of type 2 diabetes there should be evidence of insulin resistance.² The American Heart Association has suggested that a practical measure of hyperinsulinaemia is the fasting insulin level (<15 mU/l (104 pmol/l), normal; 15–20 mU/l (104–139 pmol/l), borderline; >20 mU/l (139 pmol/l), high).¹⁸ Type 2 diabetes in children was first noted in the UK in 2000.⁷ Initial cases described were all female, overweight, and of Asian or Arabic origin. More recently type 2 diabetes has been seen in white children.¹⁹

Patients with type 2 diabetes are likely to be overweight or obese using international obesity task force (IOTF) cut-offs,²⁰ with a tendency towards central fat deposition as measured by waist circumference, have a family history of diabetes, and have the metabolic syndrome (acanthosis nigricans, polycystic ovarian disease, hyperlipidaemia, hypertension, and fatty infiltration of the liver).¹⁷ Other suggestive features include a family history of insulin resistance (hypertension, abnormal lipids, polycystic ovary syndrome), lack of GAD-65 antibodies, and lack of ketonuria.² A minority of children with apparent type 2 diabetes will have autoantibodies;²¹ these patients are likely to require insulin soon after diagnosis, and may represent a latent autoimmune process.²² The UK national survey found that Pakistani children made up 21% of children with type 2 but only 2.2% of the UK child population, and Bangladeshi children were also overrepresented.^{8, 23}

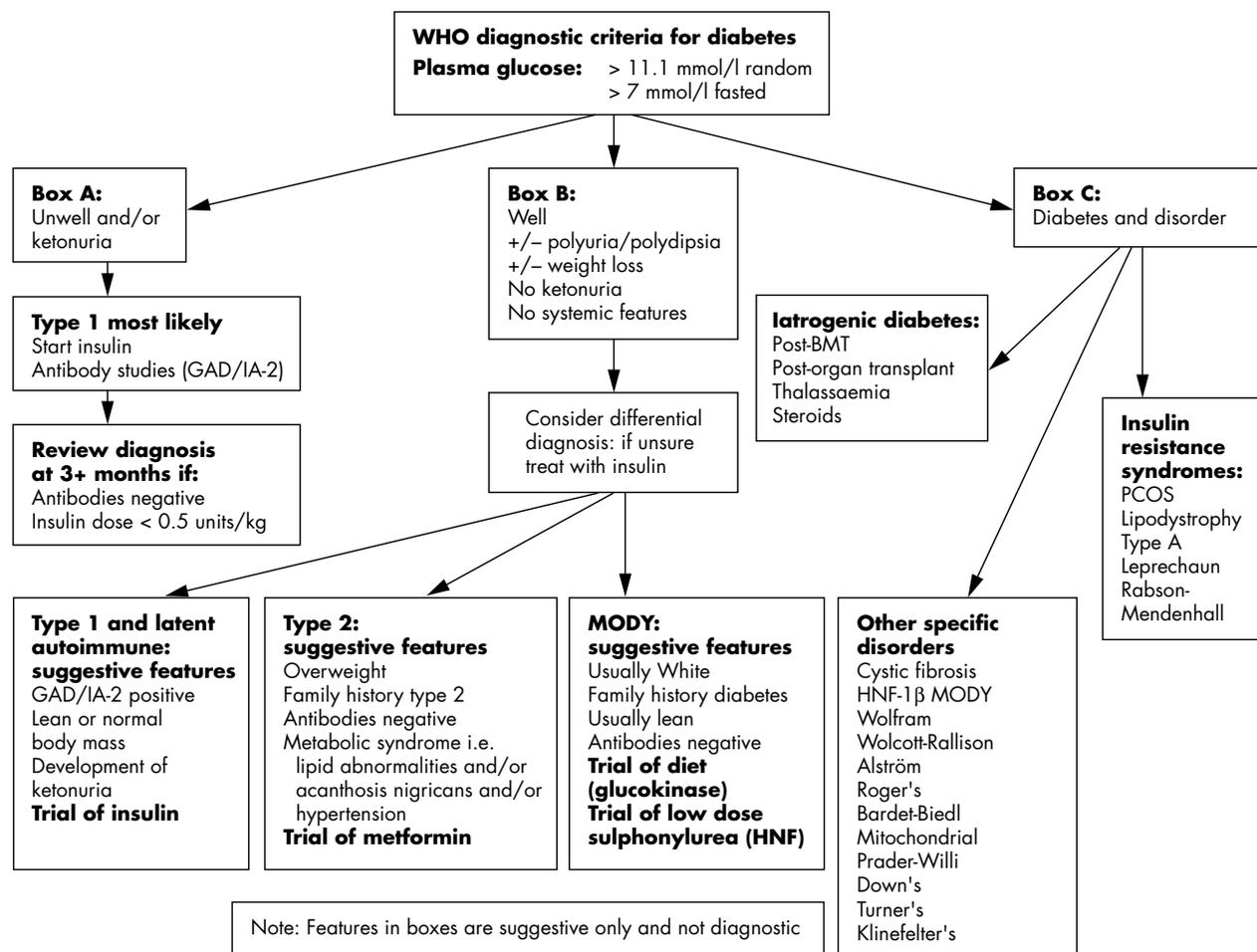


Figure 1 The presentations of acquired childhood diabetes.

Type 2 diabetes is a disorder of both β cell function and insulin sensitivity;²¹ β cell function worsens with duration of diabetes leading to insulin dependence. Insulin resistance is related to body weight in both children²⁴ and adults, and obesity (particularly deposition of visceral fat) has been linked to type 2 diabetes worldwide.^{9, 21} Ethnic groups especially susceptible to type 2 diabetes have been shown to have greater innate insulin resistance.^{17, 25}

Children and young people with type 2 diabetes have a greater risk of early retinopathy and nephropathy than those with type 1 diabetes.^{26, 27} The United Kingdom Prospective Diabetes Study (UKPDS) showed that aggressive treatment of hyperglycaemia can reduce complications.²⁸ The American Diabetes Association has published guidelines on treatment of type 2 diabetes in childhood.¹⁷ Exercise promotion and advice from a paediatric dietician should complement medical management. Drugs used in type 2 diabetes in adults fall into five groups: biguanides, sulphonylureas, thiazolidinediones, nateglinide and repaglinide, and glucosidase inhibitors. None of these drugs are licensed in childhood; however metformin, a biguanide, has been subject to a randomised control trial in adolescents,²⁹ and is being used by many clinicians as a first treatment in overweight children with type 2 diabetes. Metformin improves insulin sensitivity and is not associated with hypoglycaemia or weight gain. Side effects include gastrointestinal upset, nausea, and vomiting, and are dose dependent. We start patients on a low dose of metformin (500 mg once daily) and increase this to the maximum tolerated dose. Metformin is contraindicated in patients with renal impairment, and increases fertility in obese girls, so contraceptive advice should be given on commencement.

Hypertension, hyperlipidaemia, and proteinuria should be sought in children with type 2 diabetes and managed aggressively in conjunction with colleagues from other disciplines.

Maturity onset diabetes of the young

Maturity onset diabetes of the young (MODY) comprises a heterogeneous group of disorders caused by defects in single genes. MODY is characterised by β cell dysfunction, young onset (<25 years), and autosomal dominant inheritance,³⁰ and should be considered in non-obese patients with diabetes developing before 25 years of age and a two or three generation history of diabetes in one side of the family. MODY accounted for 15% of all non-type 1 diabetes in the BSPED survey.⁸

The first MODY gene was found in 1992,⁵ and there are now six known genes in which defects have been shown to cause MODY.³¹ These genes encode for glucokinase, which acts as a glucose sensor and five transcription factors (HNF-1 α , HNF-1 β , HNF-4 α , IPF-1, and NEURO-D1). Transcription factors are proteins that bind to promoter regions of genes and activate transcription into messenger RNA. They initiate the production of proteins which are important in the development of the pancreas.³² Each genotype produces a unique phenotype.^{31, 33} In the UK hepatocyte nuclear factor 1 α (HNF-1 α) accounts for 63% of MODY, glucokinase 20%, and other known genes <5%;³³ 15–20% of MODY patients do not have a known MODY mutation and are termed MODY X.^{31, 33}

Heterozygous glucokinase mutations produce mild fasting hyperglycaemia (5.5–8 mmol/l).³⁴ Patients may be diagnosed co-incidentally, and so may present at any age. Homozygous glucokinase defects are a rare cause of permanent neonatal diabetes.³⁵ HNF-1 α mutation carriers usually have normal blood glucose levels until the teenage years when diabetes presents. If a child with an HNF-1 α mutation is born to a mother who is diabetic they may present with diabetes considerably earlier.^{36, 37} Patients with glucokinase mutations

have glucose values that alter little with age, they have a low risk of complications, and probably do not need long term follow up. In contrast HNF-1 α patients have an inexorable β cell impairment; the progressive nature of the diabetes means that many patients will eventually require insulin and are at risk of microvascular complications.³³ Both glucokinase and HNF-1 α patients may respond to diet, and HNF-1 α patients are particularly sensitive to sulphonylureas.³⁸ Patients with HNF-1 α may be initially managed on diet alone; low dose sulphonylurea (for example, gliclazide 20 mg once daily) can be added when HbA1c levels rise.

Patients with HNF-1 β mutations have associated renal cystic disease. This can vary from single kidney involvement to severe urogenital disease. Renal disease usually precedes the development of diabetes.³⁹

MODY patients, and genetic testing can be discussed with the MODY diagnostic centre at Peninsula Medical School Exeter (see appendix).

Latent autoimmune diabetes

Latent autoimmune diabetes is the term used for patients with antibodies consistent with type 1 diabetes, but diabetes that behaves initially as non-insulin requiring. This is generally considered to be an adult disease, but there is evidence to suggest that up to 10% of children with type 2 diabetes have antibodies and so could be classified as having latent autoimmune diabetes.⁴⁰ The importance of this diagnosis is in the prediction of insulin requirement. It has been shown that GAD-65 positivity predicts an insulin requirement within three years.²²

DIABETES AND DISORDER (FIG 1, BOX C)

This is intentionally a category that encompasses many different but rare diseases. Children in this category may be already under investigation for developmental delay or single organ pathology, or may have had treatment that could predispose to diabetes. These children may be assessed within several specialties without the different problems of the child being seen in the context of a single disorder. There are some classical presentations that should prompt consideration of specific disorders (table 2).

Cystic fibrosis related diabetes (OMIM 219700)

Cystic fibrosis related diabetes (CFRD) is the commonest form of secondary diabetes, and is becoming commoner with the improved life expectancy in cystic fibrosis. Diabetes is seen in up to 34% of children with cystic fibrosis.⁴¹ CFRD tends not to be associated with ketosis, presumably because of retained basal insulin secretion. Children with CFRD have increased hepatic glucose production which is less suppressed by insulin than in controls,⁴² and this is compounded by peripheral insulin resistance.⁴³ One of the main problems with CFRD is that children are not usually symptomatic. Diabetes should be suspected in children with cystic fibrosis who show deterioration in lung function or body mass index without response to antibiotics. In the USA screening is by random glucose annually, followed by fasting glucose in those where the random glucose is greater than 7 mmol/l, but more intensive screening may be justified.^{44, 45}

Microangiopathic changes develop in CFRD with the improved survival.⁴⁶ The development of CFRD is associated with worse outcome in cystic fibrosis, and early treatment with insulin can reverse the associated decline in lung function and body mass index.⁴⁷ Most patients with CFRD are managed with insulin, but other hypoglycaemic agents are being trialled. For a more in depth review of diagnosis and treatment of CFRD the reader is referred to Mackie's excellent recent review.⁴¹

Table 2 Presentations of non-type 1 diabetes subtypes

Presentation	Diabetes type	Investigations
Overweight May have ketoacidosis Insulin dose (<0.5 units/kg) +/- Acanthosis +/- Non-white	Type 2	OGTT off insulin GAD/IA-2 antibodies
Diabetes Dominant family history Usually lean Usually no ketonuria	MODY HNF-1 α Glucokinase	Genetic analysis
Neonatal diabetes	UPD 6 Glucokinase Pancreatic agenesis Kir 6.2 mutations	Genetic analysis Genetic analysis Ultrasound Genetic analysis ⁷⁹
Liver/renal impairment in diabetic child and/or Cardiomyopathy	Wolcott-Rallison Alström	x ray hips Ophthalmic and cardiac review
Diabetes and visual impairment	Alström Wolfram Bardet-Biedl	Ophthalmic review
Deafness, diabetes, and family history	Wolfram 3243 mitochondrial mutation	Ophthalmic review Genetic analysis
Megaloblastic anaemia and diabetes +/- hearing defect	Roger	Hearing test Trial of thiamine Genetic analysis
Short stature and diabetes	Alström Turner Bardet-Biedl	Ophthalmic and cardiac review Karyotype Ophthalmic review

Down's syndrome diabetes

There have been reports suggesting an increased risk of diabetes in Down's syndrome.⁴⁸⁻⁴⁹ Diabetes in Down's syndrome is autoimmune in origin and is similar to type 1 diabetes. Features that differ from type 1 diabetes are the earlier presentation of diabetes, and low prevalence of HLA-DR3 and HLA-DR4.⁵⁰ Most children present acutely and treatment should be as for type 1 diabetes. Autoimmune thyroid and coeliac disease are more common in Down's syndrome patients with diabetes, than type 1 diabetes alone; guidelines for appropriate screening are available from the Down's syndrome medical interest group (www.dsmig.org.uk).

Insulin resistance syndromes

Insulin resistance syndromes can be thought of as a spectrum, with the metabolic syndrome at one extreme and severe life threatening disorders such as Rabson-Mendenhall at the other. Individuals may cross over between syndromes; so a girl may present with type 2 diabetes, then develop hypertension due to the metabolic syndrome, and later have problems with fertility due to polycystic ovarian syndrome.

Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) should be suspected in girls with menstrual disturbance, acne, and hirsutism. Ovarian cysts may not always be present, and raised testosterone and LH levels alone can be diagnostic.⁵¹ PCOS has increasingly been recognised as a disorder of insulin sensitivity. Metformin and other insulin sensitising agents have been used with success in adults with PCOS, to regulate the menstrual cycle.⁵² Metformin has been shown to be safe in adolescents with type 2 diabetes,²⁹ and is therefore the preferred choice in PCOS. Recent evidence suggests that the

use of metformin in girls with premature pubarche and hyperandrogenism at menarche can prevent the development of PCOS.⁵³ Metformin should be used in conjunction with lifestyle modification, and treatment for dysmenorrhoea (for example, oral contraceptives) and hirsutism.⁵²

Other syndromes of insulin resistance

Insulin resistance and diabetes are seen in lipodystrophy syndromes, and defects of the insulin receptor. Lipodystrophy syndromes range from severe neonatal diabetes to more subtle partial lipodystrophies, which may not present till adolescence. Donohue syndrome (previously known as leprechaunism) presents with severe intrauterine growth restriction, lipodystrophy, and fasting hypoglycaemia with postprandial hyperglycaemia. Most patients die within the first year. Rabson-Mendenhall syndrome is similar but with characteristic thickened nails and dental dysplasia. Patients have progressive diabetes and most die in the first decade.⁵⁴ Type A syndrome affects lean, predominantly female adolescents with severe insulin resistance, hyperandrogenism, and acanthosis nigricans. Female patients have androgen excess ranging from mild hirsutism to frank virilisation. Diabetes or impaired glucose tolerance is one of the later manifestations of the disorder.⁵⁵ There is some evidence that metformin can be of use in type A insulin resistance.⁵⁷

These rare insulin syndromes are discussed in more detail in Tritos and Mantzoros's comprehensive review.⁵⁶

Wolcott-Rallison syndrome (OMIM 226980)

Wolcott-Rallison syndrome is a rare autosomal recessive condition characterised by extremely early onset diabetes, epiphyseal dysplasia, renal impairment, acute hepatic failure, and developmental delay. Non-autoimmune insulin deficient diabetes presents in infancy.⁵⁸ The gene for

Wolcott-Rallison has been isolated to EIF2AK3, a regulator of protein translation.⁵⁹

Wolfram syndrome (OMIM 222300)

Wolfram syndrome (previously known as DIDMOAD) is an autosomal recessive syndrome, in which the association of diabetes with progressive optic atrophy under 16 years of age, is diagnostic.⁴ Other features, which appear with age, are sensorineural deafness, diabetes insipidus, dilated renal tracts, and truncal ataxia or more protean neurological signs. Non-autoimmune insulin deficient diabetes presents in the first decade. The median age of death is 30.⁶⁰ Mutations in the Wolfram gene (WFS-1) are present in 90% of patients.⁶¹

Alström syndrome (OMIM 203800)

Alström syndrome is a rare autosomal recessive disorder characterised by short stature, early obesity, retinal degeneration, neurosensory deafness, infantile cardiomyopathy, chronic renal impairment, and diabetes mellitus.⁶² Hepatic involvement has been described. Visual and auditory impairment are progressive. Insulin resistant diabetes mellitus occurs in about 50% of patients with Alström syndrome and may respond to metformin, though most require insulin.^{62–63}

Bardet-Biedl syndrome (OMIM 209900)

The key manifestations of Bardet-Biedl syndrome are retinal dystrophy, obesity, hand abnormalities, renal abnormality, and male hypogonadism; mental retardation may also be seen. Thirty per cent of patients develop insulin resistant diabetes.⁶⁴ The syndrome is linked to seven loci, and inheritance seems to be variable, with some pedigrees showing recessive and some multigenic inheritance.^{65–66}

TRMA/Roger's syndrome (OMIM 249270)

Thiamine responsive megaloblastic anaemia (TRMA) is the association of thiamine responsive megaloblastic anaemia with insulin deficient diabetes and sensorineural deafness. Diabetes may respond to thiamine, but all patients develop an insulin requirement in the long term.⁶⁷ Mutations in SLC19A2 (a membrane bound thiamine transporter) cause this recessive disorder.⁶⁸

Mitochondrial mutations (OMIM 520000)

In 1992 a mutation in mitochondrial DNA at nucleotide position 3243 was found to segregate with diabetes.⁶⁹ This has proved to be the commonest mitochondrial mutation causing diabetes, but overall mitochondrial mutations are a rare cause of childhood diabetes. Factors that are suggestive of mitochondrial diabetes are maternal inheritance (as mitochondria are inherited exclusively from one's mother),⁷⁰ and associated deafness, myopathy, or neurological deficits. Trials of specific treatments for mitochondrial diabetes have been unpromising, and patients usually require insulin from diagnosis.⁷⁰

Iatrogenic diabetes

Thalassaemia

Thalassaemia is associated with an increased incidence of insulin resistant diabetes.⁷¹ Hyperinsulinaemia is due to increased secretion of insulin as well as reduced extraction of insulin by the iron overloaded liver. The risk of diabetes is directly proportional to the number of transfusions, and increasing age. It is unknown whether this is due to iron related β cell damage or β cell exhaustion.^{72–73} Insulin resistance increases with puberty more in thalassaemic patients than in normal adolescents, and glycaemic control deteriorates.⁷³ Adolescent thalassaemic patients should be made aware of the significance of polyuria and polydipsia as osmotic symptoms of diabetes.

Diabetes after transplantation

Glucose intolerance and overt diabetes have been increasingly recognised as sequelae of bone marrow transplantation. In a cohort of Finnish survivors 43% had diabetes or glucose intolerance >3 years after transplantation.⁷⁴ These patients, who had received total body irradiation, appeared overweight and insulin resistant, compounded by hypogonadism causing insulin resistance in patients who have had cranial irradiation.⁷⁴

Post-transplant diabetes is a recognised complication of solid organ transplant in children with a prevalence of diabetes of 3–17% in renal and thoracic organ recipients.^{6–75} Risk factors for diabetes are use of tacrolimus immunosuppression, African ethnicity, and pulsed corticosteroid therapy.⁶

Diabetes after steroid treatment

Corticosteroids cause a rise in fasting insulin levels, an increased first phase insulin response, and increased hepatic glucose production. Diabetes is a recognised complication in about 20% of patients on high dose corticosteroids.⁷⁶ Most healthy individuals will tolerate transient hyperglycaemia well during short courses of steroids, and may be managed by reduction in dietary sugar intake alone. Those with diabetes however,⁷⁷ and their relatives⁷⁸ may develop symptoms and require additional treatment.

CONCLUSIONS

The vast majority of children presenting with diabetes in the UK will have type 1 diabetes. The safest form of treatment for a newly presenting diabetic child is insulin, particularly if the child is unwell or has ketonuria. The well child with mild symptoms of diabetes is more problematic, but the balance of probabilities dictates that the overweight child from an ethnic minority is likely to have type 2 diabetes, and the slim white child is likely to have MODY, but there are non-obese, white type 2 patients and Asian MODY patients. It is important to review the diagnosis regularly if glycaemic control is difficult to achieve or other symptoms arise. It is vital to make an accurate diagnosis in these patients as the prognosis, management, impact on lifestyle, and surveillance for complications differ dramatically between the different subtypes of diabetes. Discussion with clinicians with particular interests in these less common forms of diabetes is recommended.

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APPENDIX: WHERE TO GO FOR FURTHER INFORMATION

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- Prof. A Hattersley, Peninsula Medical School Exeter; a.t.hattersley@ex.ac.uk, www.diabetesgenes.org
 - Special interest in MODY, mitochondrial disease, and ISPAD rare diabetes project

- Dr S O'Rahilly, University of Cambridge; sorahill@hgmp.mrc.ac.uk
 - Special interest in insulin resistance syndromes
- Dr J Shield, University of Bristol; j.p.h.shield@Bristol.ac.uk
 - Special interest in neonatal diabetes, Down's syndrome and diabetes, mitochondrial disease, obesity and type 2 diabetes

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