

The Child with Diabetes Mellitus

CLASSIFICATION AND PHYSIOLOGY

Diabetes mellitus is present when the blood sugar level is greater than 11 mmol/L on a random blood sample (or at 2 h in a glucose tolerance test; see Appendix) or greater than 7 mmol/L on a fasting sample. Random values between these figures suggest 'impaired' glucose tolerance. Children may show occasional values of more than 11 mmol/L after severe stress, such as a convulsion, but in the absence of a suggestive history and with prompt return to normoglycemia the diagnosis of diabetes should not be made in these cases. There is some evidence that a proportion of these children with stress-induced hyperglycemia are at risk of later diabetes, but it is not usual to institute further investigations and follow-up outside research programs.

Diabetes mellitus results from a relative deficiency of insulin, which is required for normal glucose homeostasis. Insulin is secreted as a single-chain polypeptide called pro-insulin from the beta cells of the pancreas. This is cleaved to yield insulin and C peptide, both of which enter the circulation. Plasma C-peptide levels indicate the residual insulin production by the pancreas, as there is no C peptide in commercially manufactured insulin. The release of insulin is controlled largely by glucose entry into the beta cell via an active transport mechanism (Glut2). This leads to a rise in intracellular adenosine triphosphate (ATP) levels and the closure of a two-component potassium channel (Kir6.2 and Sur1). In turn this leads to membrane depolarization and influx of calcium through a voltage-dependent calcium channel. Exocytosis of insulin is stimulated from storage granules, and insulin is released into the portal circulation.

The rate of insulin production and release is determined mainly by the level of blood glucose, a rise in the blood glucose concentration causing a rise in insulin production. Amino acid levels rise after eating and also stimulate insulin secretion, controlled by a number of different gut hormones such as gastric inhibitory polypeptide (GIP).

Insulin is removed rapidly from the plasma, with a half-life of about 4 min. Insulin normally causes synthesis of glycogen, protein, triglycerides and glucose oxidation. Thus a relative deficiency causes a rise in

blood glucose levels and ketones along with reduced glucose oxidation. This in turn leads to a rise in blood glucose concentration, glycosuria when the renal threshold is exceeded, an osmotic diuresis and dehydration, wasting of fat and muscle, and ketosis.

Several other hormones have an effect on blood glucose levels. Amylin is a small 37-amino-acid peptide co-secreted with insulin that controls gastric emptying and hepatic glucose release. Resistin is a 750-amino-acid peptide hormone (coded by a gene on chromosome 19) secreted from white fat that modifies insulin sensitivity in the periphery. In humans it is more highly expressed by fat from central rather than peripheral sites. Tumor necrosis factor (TNF) α is a cytokine secreted by adipocytes that may also modify insulin sensitivity. Glucagon, growth hormone, cortisol and epinephrine (adrenaline) all produce a rise in blood glucose concentration by inhibiting glucose uptake by muscle and by stimulating the production of glucose from amino acids, glycerol and glycogen stored in the liver. Epinephrine also inhibits insulin release from the pancreas. During fasting, the blood sugar and amino acid levels fall, and this results in a fall in insulin levels. However, there is a rise in glucagon, growth hormone and cortisol levels, producing an increase in the breakdown of glycogen and in blood glucose production from lactate, amino acids and glycerol. These counter-regulatory hormones continue to operate even in a child with diabetes (certainly during the early phases of the illness) and will be produced in response to hypoglycemia.

Diabetes mellitus can be produced in a number of different ways. Type 1 diabetes is caused by immune-mediated or idiopathic islet cell destruction, resulting in insulin deficiency. In type 2 diabetes there is a relative insulin resistance or a combination of insulin resistance with a secretory failure. Type 3 diabetes includes several different mechanisms for abnormal glucose homeostasis: genetic defects of beta-cell function and insulin action, diseases and infections of, and toxicity to, the exocrine pancreas, defects in counterregulation caused by other endocrine disorders, immune-modulated conditions, and associations with genetic syndromes. Type 4 diabetes (gestational diabetes) is not considered in this chapter.

TYPE I DIABETES

EPIDEMIOLOGY OF CHILDHOOD DIABETES

The incidence of type 1 diabetes varies considerably across the world, being highest in the Scandinavian countries (>20 per 100 000 population per year), intermediate in countries such as the UK, USA and New Zealand (7–19 per 100 000 per year), and lowest in Asian and South American countries (<7 per 100 000 per year). Finland has the highest incidence in the world (43 per 100 000 per year) where the risk is 60 times greater than in China, which has the lowest incidence (0.7 per 100 000 per year). In temperate latitudes about 2–3 per 1000 children aged under 16 years are affected by childhood diabetes, so it is a relatively uncommon disorder in primary care. The incidence is slowly rising in the Western world. When families migrate from an area of low incidence to one where the disease is common, they acquire the risk of their new homeland, suggesting an environmental trigger.

Type 1 diabetes is very rare in the first few months of life, the incidence rising from 9 months of age until puberty, with a fall in adult life. There are peaks occurring at around 5 years of age and again at around the time of puberty, and these patterns are seen around the world. A seasonal variation has been observed worldwide, with a reduction in the warm summer months. The northern and southern hemispheres are 6 months out of phase. These patterns indicate that triggers such as virus infections may be important. However, there is also evidence of an important genetic contribution in the development of diabetes as a first-degree relative with insulin-dependent diabetes mellitus (IDDM) increases the risk to 3–10%, and in monozygotic twins the concordance rate is 36%. Although the risk of developing diabetes is roughly equal for males and females, the inheritance of risk is less from a mother with IDDM (2%) compared with a father with IDDM (6%).

Chromosome 6 carries genes encoding for human leukocyte antigens (HLAs) expressed on the surface of most nucleated cells and they present processed antigens to cytotoxic T lymphocytes. A strong relationship has been demonstrated between type 1 diabetes and the HLA-DR locus, with approximately 95% of IDDM cases having either DR3 and/or DR4 antigens. Some HLA types are 'protective' (i.e. 2 and 5). There is some variation in phenotype with different HLA type; for instance, DR3 has more of an association with other autoimmune disease and a longer honeymoon period in comparison with that in patients with DR4, who are also younger. If individuals are positive for both DR3 and DR4, their risk of diabetes is 25%.

Antibodies against pancreatic islet cells (islet cell autoantibodies; ICAs) and insulin have been detected in 65–100% of newly diagnosed patients with IDDM. As yet it is not known whether these antibodies play a direct role in the disease process or whether they serve simply as a marker for damage by other etiologic agents. However, fewer than 50% of ICA-positive individuals develop IDDM, so it is likely that other genetic and environmental factors influence the development of the disease. Anti-glutamic acid decarboxylase (anti-GAD) antibodies are even more sensitive markers for the development of type 1 diabetes than ICAs. They may be detected up to 10 years before the onset of the disease and persist for longer than ICAs, which may disappear after several years of the disease.

A number of different environmental triggers has been proposed. Viral infections such as retroviruses and coxsackie B4 have been implicated, but are not identified in the majority of IDDM cases. There does appear to be some evidence for nutritional triggers. An increased incidence of IDDM has been demonstrated in rats with early exposure to cow's milk protein, and in Scandinavia the incidence is significantly higher in children who were fed on formula from an early age. It is suggested that a whey protein, bovine serum albumin, is conformationally similar to a surface protein of beta cells of genetically susceptible children, thus sensitizing the immune system. At times of stress or viral infection, the pancreas is exposed to the sensitized immune system and anti-islet cell antibodies are produced, leading to beta-cell destruction.

After presentation there is commonly a phase of relatively preserved post-meal insulin secretion, the 'honeymoon phase', which may persist for months to 1–2 years before insulin production ceases totally.

PRESENTATION OF TYPE I DIABETES

The so-called 'classical triad' of diabetes is:

- polyuria.
- polydipsia.
- weight loss.

Less commonly (5% in a recent series) in the developed world the child may present with diabetic ketoacidosis (DKA), usually at a time of intercurrent illness or hot weather. DKA may present classically with acidotic, ketone-laden respiration and dehydration, but can sometimes present as shock, acute abdominal pain or an apparent respiratory illness (**Figs 10.1 & 10.2**).

In retrospect the child will have been lethargic, miserable and may have suffered from candidiasis or recurrent staphylococcal skin infections. There may be

Fig. 10.1 Severe diabetic ketoacidosis and dehydration.



Fig. 10.2 The same child as in Fig. 10.1, 4 months later.

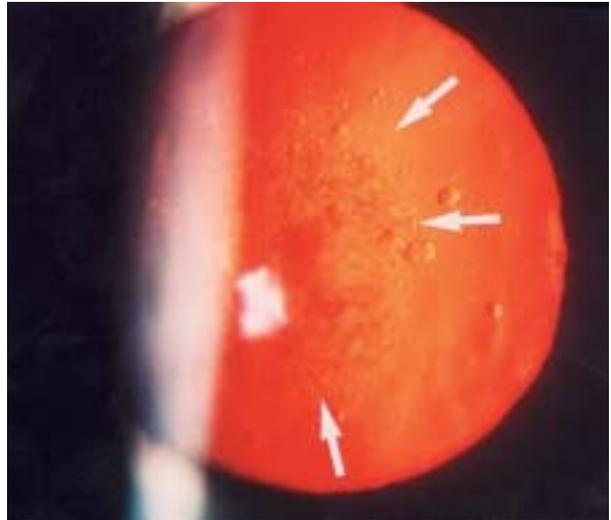


Fig. 10.3 Posterior subcapsular cataract at presentation of diabetes.

and education are undertaken at home. This increases the family's confidence to manage their child's diabetes and reduces the 'medicalization' of the disease. Other centers feel that a prolonged admission for initial education results in later improved control. Local circumstances will dictate the appropriate approach.

Subsequent outpatient care should include frequent multidisciplinary follow-up from physicians, specialist nurses, dieticians and psychologists. Ideally an age-banded clinic allows for the differing educational, physiologic and psychologic needs of the child to be provided in a planned and logical manner. This is particularly true of adolescence, when there is often particular resistance to external control and resentment of perceived differences from peers.

Educational 'camps' and holidays are organized in many countries and allow for peer-led education and direct experience of coping with vigorous exercise (Fig. 10.4).

Education

The most important component of management is education, to empower the family and child to care for their own diabetes and make adjustments to diet and insulin in response to changes in daily activity, growth and health. The most predictive factors about long-term control relate to the abilities and stability of the family and child, and the degree of support they receive from a multidisciplinary medical team. The education should be age and language appropriate and delivered frequently at a rate that can be assimilated by the family. It needs to include other carers, the school and leisure

secondary nocturnal enuresis. If there is a long prodromal phase, there may be cataracts at presentation (Fig. 10.3).

Type 1 diabetes is not infrequently diagnosed by the serendipitous demonstration of glycosuria during attendance at primary care or by 'screening' of children with previously affected relatives.

MANAGEMENT OF THE CHILD WITH NEWLY DIAGNOSED TYPE I DIABETES

Some studies have demonstrated there is a lower readmission rate in families where the early management



Fig. 10.4
Participant in diabetes education camp learning self-injection.



Fig. 10.5 Three methods of insulin administration: conventional low-volume syringe with high-gauge needle; insulin 'pen' with cartridge; pump for continuous subcutaneous insulin infusion (CSII).

organizations. Ideally patients should be able to inject insulin as needed for their diet and activity, and make appropriate adjustments to maintain as near-normal sugar levels as is possible without severe hypoglycemia.

Insulin

In most developed countries biosynthetic human insulin is used. Of the unmodified types there are basically two forms: 'short acting' or 'medium-long acting'. Short-acting insulin is, in reality, a misnomer because it forms a hexameric crystal that must dissociate to a monomer to be active, and has a peak of action at around 2–4 hours if given subcutaneously, lasting for 8 h post-injection. These insulins are used as 'bolus' injections with food (although now being replaced by genetically modified insulins; see below) or mixed with the longer-acting varieties and given two or three times a day.

Increased absorption time is created by binding insulin to a simple peptide, protamine, to form the isophane insulins or to crystallize the insulin in the presence of zinc to form the lente insulins (the bigger the particles formed, the longer the half-life). Isophane insulin, being bound 1 : 1 to protamine, can be mixed in various ratios with soluble insulin to derive pre-mixed preparations. The excess of zinc in the lente insulins combines with soluble insulin to delay its action, and so must be mixed by the patient shortly before administration. These insulins have peaks of action after 4 h and may persist for 18–24 h after injection. Mostly they are designed to be given twice a day.

Modern genetically modified insulins are becoming widely available in both truly short- and long-acting

forms. In the short-acting modified insulins there are amino acid substitutions that result in conformational changes that inhibit crystal formation and hence remain monomeric. The speed of action is around 1 h to peak, with an action to 4–6 h depending on the preparation used. They are very suitable for bolus injection, as required to normalize sugar levels, and for use in pumps (see below). The long-acting modified insulins are altered to change their solubility at physiologic pH levels and precipitate in tissue after injection to form a reservoir, which effectively provides a constant background level.

Insulin (**Fig. 10.5**) can be administered parenterally, usually by subcutaneous injection, or intravenously in DKA. High-gauge needles and low-volume syringes make the injection relatively painless, and the injection may be packaged as a pen device for patient convenience. Pressurized sprays are sometimes used as an alternative to needles. Increasingly, continuous subcutaneous infusions of (modified short-acting) insulin (CSII) are used with a programmable external pump which can be set at different rates for day and night, and also used to deliver boluses of insulin with food. Inhaled insulin is being currently investigated for safety and efficacy, delivered at around 10 times the subcutaneous dose by a special inhaler device for bolus use.

The exact insulin regimen chosen needs to be modified to be appropriate for the age and capabilities of the child and family. In young children with a persistent honeymoon period, twice-daily medium-acting insulin may be all that is required for the first few years. After the honeymoon, short-acting insulin will be required to cover the post-meal peaks of glucose and can be

delivered pre-mixed with medium-acting insulin in various combinations or as individual boluses tailored to the carbohydrate content of the meal or snack (in which case twice-daily medium–long-acting insulin will be required for ‘basal’ cover).

Islet cell transplants, either from cadaveric donors or from modified animal tissue, are being investigated as a curative treatment for type 1 diabetes, but are not yet available for use in children.

A usual starting dose of insulin is around 0.5 units per kg per day. In puberty, requirements may climb to 2 units per kg per day, before settling by 50% at sexual maturity.

Diet

A high-fiber, high-carbohydrate (50–55% of calories), low-fat (35% of calories) diet is recommended. This may be prescribed as ‘portions’ appropriate for the age and growth of a child, or given more liberally as a ‘healthy’ diet. There is some evidence that the ability to match specific input to bolus levels of insulin results in better control, but this requires considerable training to achieve. If twice-daily insulin regimens are used, carbohydrate must be eaten at three main meals and at three snacks – mid-morning, afternoon and bedtime – to prevent the unopposed action of insulin and therefore hypoglycemia between main meals.

Monitoring control

To vary insulin dosage sensibly, the patient must be able to test blood (or sometimes urine) glucose levels. Modern lancets and finger-pricking devices, coupled with rapid-reading meters, make this easier than in previous times, but monitoring remains one of the main barriers to achieving good control in childhood. Sensible, achievable goals for control need to be set (particularly in adolescence) and there is evidence to suggest that the best control is possible only with frequent testing (and then subsequent alteration of insulin dose or diet).

In the longer term, measurement of glycosylated hemoglobin levels (HbA1c) is required to assess the risk of complications (see below). All proteins are glycosylated at the time of synthesis in proportion to the ambient glucose level. Other proteins have been used (e.g. serum albumin, fructosamine), but most information regarding risk is related to HbA1c and this is becoming the standard test. The red cell extrudes its nucleus as it leaves the bone marrow, halting hemoglobin synthesis. A sample of blood will therefore include a population of cells from 0 to 120 days of ‘age,’ and the HbA1c level (the percentage of the hemoglobin A1c fraction on chromatography that is glycosylated)

will represent the average control over this period (with a bias to the first 40 days). The normal range is usually less than 6%, but caution should be used in interpreting levels in populations or patients that may have abnormal hemoglobin (e.g. HbF) due to hemoglobinopathies. The Diabetes Control and Complications Trial (DCCT) showed that the risk of complications is related to HbA1c level in a curvilinear fashion, with rapidly increasing risk of retinopathy and nephropathy after 8% and an approximate doubling of risk for every percentage point thereafter.

Hypoglycemia

A relative excess of insulin for the dietary intake of the child or energy expenditure may result in rapid hypoglycemia. Early warning symptoms vary from child to child but include pallor, tremor, hunger, change in mood and sweating. The blood sugar level needed to produce these symptoms is very variable. Some children with poor long-term control may feel ‘hypo’ at levels of 7 to 8 mmol/L. In patients with excellent long-term control and frequent hypoglycemic episodes, this early warning may be lost and occur only at the same time as CNS symptoms. CNS signs with a reduced level of consciousness leading to coma and convulsions reliably occur as the blood sugar level drops below 2.6 mmol/L.

Nocturnal hypoglycemia is extremely common in childhood, although often unrecognized (Fig. 10.6). It may produce nightmares, bed-wetting or morning headaches secondary to unrecognized convulsions.

The DCCT showed that the risk of hypoglycemia was inversely related to HbA1c level, although patients do get better at predicting hypoglycemia with experience. Young children with a growing brain are particularly at risk of CNS damage from severe hypoglycemia in the first 5 years of life. This may result in later learning difficulties and epilepsy.

Treatment of hypoglycemia is by a staged approach (Fig. 10.7). Initially a short-acting sugary drink or snack should be eaten, followed by a complex carbohydrate meal or snack. If the child is uncooperative because of the hypoglycemia, then sugary gel can be placed in the mouth or, if consciousness is being lost, glucagon can be administered to raise sugar levels (although this often results in vomiting and so parenteral dextrose may be subsequently required).

Sick-day rules

During illness counterregulatory hormone levels rise and lead to an increase in blood glucose concentration. The child is at high risk of ketoacidosis during illness. Insulin must always be given during illness, even if the child is eating little, although the dose may need to be

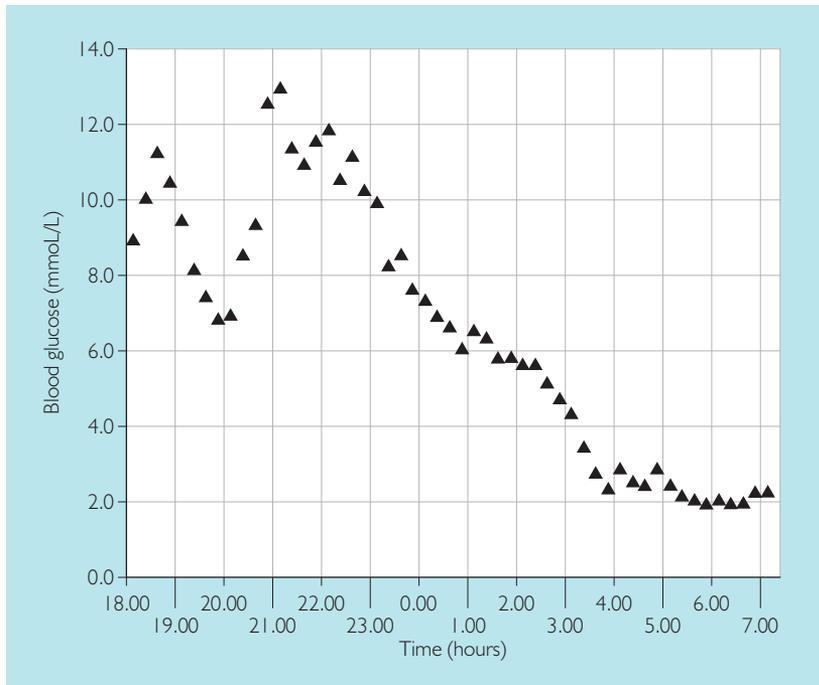


Fig. 10.6 Overnight blood glucose profile showing unrecognized asymptomatic hypoglycemia from 0400 to 0600hours. Such profiles are found commonly in childhood. (Data courtesy of Professor David Dunger.)



Fig. 10.7 Staged approach to hypoglycemia (food; dextrose tablets or sugary drink; dextrose polymer gel; glucagon).

reduced in gastroenteritis. Glucose-containing food and drink should be offered frequently and the blood glucose levels checked regularly, along with urinary ketones. Rising levels of sugar and ketosis should prompt seeking medical advice.

Psychological support

Many parents go through a period of ‘bereavement’ following the diagnosis of diabetes in their child, including the classic feelings of guilt, denial, anger and disbelief. Young children and adolescents in particular may find it very difficult to come to terms with their

illness. Diabetes affects not just the child but the whole family, and other siblings must also be considered. Access to expert psychological support is hence vital.

Complications

Clinically significant complications of diabetes are rare in childhood, although joint stiffness (see Fig. 1.22) may be seen after only a few years of diabetes due to glycosylation of collagen. Lipohypertrophy is common if the injection sites are not ‘rotated’ frequently (Figs 10.8 & 10.9). As the hypertrophied site becomes relatively anesthetized, there is a vicious circle of continuing use and subsequent poor absorption of insulin. More rarely, lipodystrophy can occur, even with sole use of human insulin (Fig. 10.10).

Diabetic nephropathy is predicted by the appearance of macroalbuminuria (>300 mg albumin per 24 h); 50% of patients will develop renal failure within the next 10 years. Some 40% of patients may develop renal complications that can occur any time after 5 years of diabetes, but usually after 15 years of age. Microalbuminuria is the presence of >30 mg and <300 mg albumin per 24 h in the urine, which may also be detected on screening early morning urine and measuring an albumin : creatinine ratio. A ratio greater than 4 requires further investigation. However, in children, unlike adults, the presence of microalbuminuria may be variable and not as predictive of later progression of renal involvement, and so should be

Fig. 10.8
Lipohypertrophy
of abdomen.



Fig. 10.10
Lipoatrophy of
buttocks.



Fig. 10.9 Lipohypertrophy of arms.

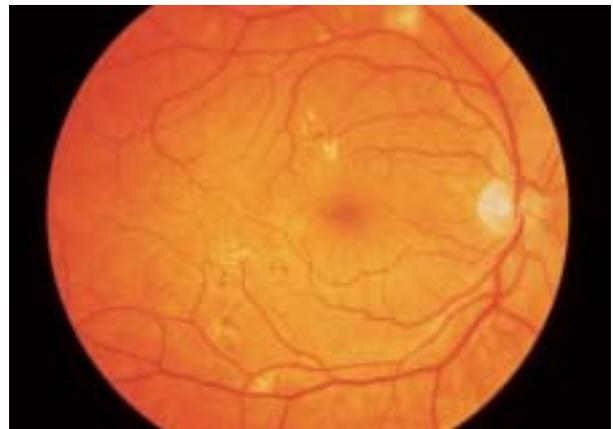


Fig. 10.11 Mild diabetic retinopathy found at presentation of childhood type I diabetes.

treated only if persistent or accompanied by hypertension. The evidence that angiotensin converting enzyme (ACE) inhibitors prevent or slow the progression of nephropathy in children is not available.

Diabetic retinopathy (**Fig. 10.11**) may rarely be present at, or soon after, presentation in some individuals, presumably representing an inherent genetic susceptibility to this complication. Usually it occurs after 5 years of diabetes and in the teenage and young adult years when detectable changes become almost universal. Only the minority of these changes will require laser photocoagulation, however. All patients should have their dilated fundi examined yearly after 5 years of diabetes, and teenagers. Diabetic posterior subcapsular cataract may be seen at presentation in children who had

a long prodromal phase, and this should be looked for at diagnosis (**Fig. 10.3**).

Skin manifestations of diabetes tend to be non-specific as they can occur alone or in combination with other systemic disorders, but include necrobiosis lipoidica (**Fig. 10.12**) and granuloma annulare (**Fig. 10.13**), which are seen more frequently in type 1 diabetes.

Other autoimmune conditions occur with increased frequency, such as Hashimoto disease (in >5%), vitiligo and systemic lupus erythematosus (SLE) (see **Figs 9.2, 9.3 & 9.7**) as well as rheumatoid arthritis (**Fig. 10.14**). Regular (4–5 yearly) measurement of antithyroid antibody status and further yearly checking of thyroid stimulating hormone (TSH) levels in antibody-positive



Fig. 10.12 Necrobiosis lipoidica.



Fig. 10.13 Granuloma annulare.

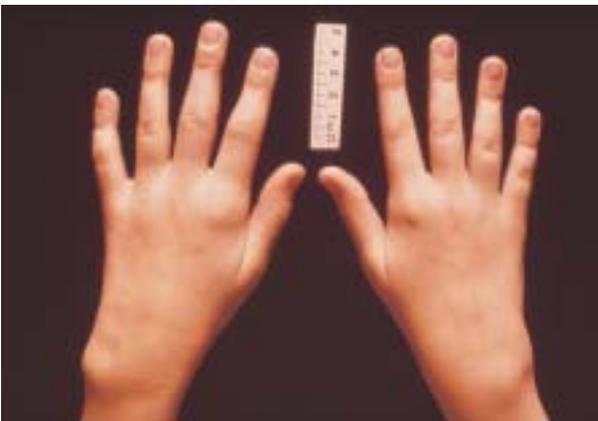


Fig. 10.14 Rheumatoid arthritis in association with type 1 diabetes.

individuals is routine in many clinics. Adrenal antibody-positive Addison's disease developing in a child with type 1 diabetes is rare, but serious, and may present with unexplained hypoglycemia and weight loss. Celiac disease is sufficiently common (2–4%) for some clinics to

recommend screening by regular measurement of endomysial antibodies. It is commonly asymptomatic when detected this way and there is little evidence for the long-term benefit of an extra dietary therapy in these cases. Certainly all children with type 1 diabetes and gastrointestinal symptoms or unexplained weight loss should have their serology checked.

Mauriac syndrome secondary to long-term poor control is now rarely seen in the developed world, although it still occurs in those areas where insulin supply is limited for economic reasons (see **Figs 4.17 & 4.18**).

Diabetic ketoacidosis

The treatment of DKA is outlined in the notes and algorithm shown in **Fig. 10.15**.

TYPE 2 DIABETES

There is no specific diagnostic test for type 2 diabetes, and its diagnosis in childhood is often confirmed only in retrospect. Some patients with type 1 diabetes have a slow evolution and may manage without insulin for months after diagnosis. In some children with one of the type 3 maturity-onset diabetes of youth (MODY) syndromes (see below) it may be impossible initially to delineate a mutation or exact phenotype because of the heterogeneity of the condition. Classically a child with type 2 diabetes will be overweight (**Fig. 10.16**), have signs of insulin resistance (acanthosis) (**Fig. 10.17**) and a positive family history of type 2 diabetes in one or more first-degree relatives. Type 2 diabetes is much commoner in some ethnic groups (from the Indian subcontinent and Mexico, in particular). On testing they will not be DR3/4 positive, will be islet cell and GAD antibody negative and may have a raised fasting insulin: glucose ratio. They remain C-peptide positive for many years. The associated features of dyslipidemia and hypertension may already be present in childhood.

The role of the recently discovered hormone, resistin, in type 2 diabetes remains to be elucidated, but this secretion from white fat, along with free fatty acid and TNF- α release, appears to modulate peripheral insulin resistance and may explain partly the link between type 2 diabetes and obesity. A failure of insulin secretion may follow a period of insulin resistance, making retrospective diagnosis of type 2 diabetes very difficult. The inheritance is polygenic with some gene polymorphisms appearing important in particular populations, but not others.

Type 2 diabetes used to be extremely uncommon in children but its incidence is rising along with the incidence of obesity and inactivity.

TREATMENT OF TYPE 2 DIABETES

Lifestyle modification, with increased exercise in particular, is important. Muscle can clear glucose more efficiently in the active child and this contributes as much as oral drug therapy to control. A diet should be introduced that comprises a high unrefined carbohydrate, low fat intake and is coupled with weight stabilization or reduction as appropriate. If glycosylated hemoglobin levels can be maintained at a satisfactory level, initially exercise and dietary therapy may be all that is required. If control is poor, then monotherapy should be initiated with an oral hypoglycemic agent. Metformin is probably the drug of choice as it has anorectic properties, no hypoglycemia risk and is usually well tolerated (although gastrointestinal side effects may limit the dose used). Metformin acts by reducing hepatic glucose production and increasing peripheral insulin sensitivity. It also has a role in restoring ovulation in those obese girls with a polycystic ovarian phenotype in addition to their diabetes. Sulfonylureas have the advantage of once-daily dosing, but may lead to weight gain and hypoglycemia. They act by increasing insulin release from the pancreas. Dual therapy with metformin and sulfonylureas may subsequently be required, and the place of newer agents such as the glitazones (insulin ‘sensitizers’), repaglinide (post-prandial insulin secretagogues) or acarbose (an α -glucosidase inhibitor that slows down glucose absorption from food), alone or in addition to one of the older agents, has yet to be established in children, although their effect on control is likely to be small. If

HbA1c is consistently high, insulin may be required as for type 1 diabetes.

TYPE 3 DIABETES

The commonest genetic defects of beta-cell function are often called the maturity-onset diabetes of youth (MODY) syndromes. There are currently at least six subtypes caused by different mutations, usually transmitted in a dominant fashion. They are characterized by a primary defect in insulin secretion and the onset of often mild non-ketotic diabetes at age less than 25 years in the context of a familial history. The onset may be at younger ages in successive generations. The patients are DR3/4 negative and antibody negative, and remain C-peptide positive. Treatment is usually dietary, but some forms may require metformin or insulin therapy. Sulfonylureas may produce severe hypoglycemia, especially in type 3 MODY. **Table 10.1** shows the various currently recognized subtypes of MODY, although new mutations are being described.

Mitochondrial DNA abnormalities can also result in defects of beta-cell function and should be suspected if diabetes, neuromuscular and retinal abnormalities such as retinitis pigmentosa (see **Fig. 1.117**) coexist in a child.

Genetic defects of insulin action can result from defects in the insulin receptor, or post-receptor signaling (and, extremely rarely, from structural abnormalities of insulin itself, although most described cases are euglycemic). In type A insulin resistance there is an

Type 3a diabetes – maturity-onset diabetes of youth (MODY) subtypes

	Genes	Severity	Other
MODY 1 and 3	<i>HNF4</i> and <i>HNF1α</i>	Similar; worsen with age and may become severe	May progress from oral agents to insulin. Complications occur
MODY 2	Glucokinase	Mild	Dietary treatment. Homozygous state results in permanent neonatal diabetes
MODY 4	<i>IPF1</i>	Very rare, mild. Beta-cell development altered	Homozygous state causes pancreatic agenesis
MODY 5	<i>HNF1β</i>	Moderately severe	Diabetes and renal cysts. Female Müllerian abnormalities
MODY 6/others	Various transcription factors	Moderately severe	May account for more than 50% of cases of MODY in some populations

Table 10.1 Type 3a diabetes – maturity-onset diabetes of youth (MODY) subtypes

Algorithm for treatment of diabetic

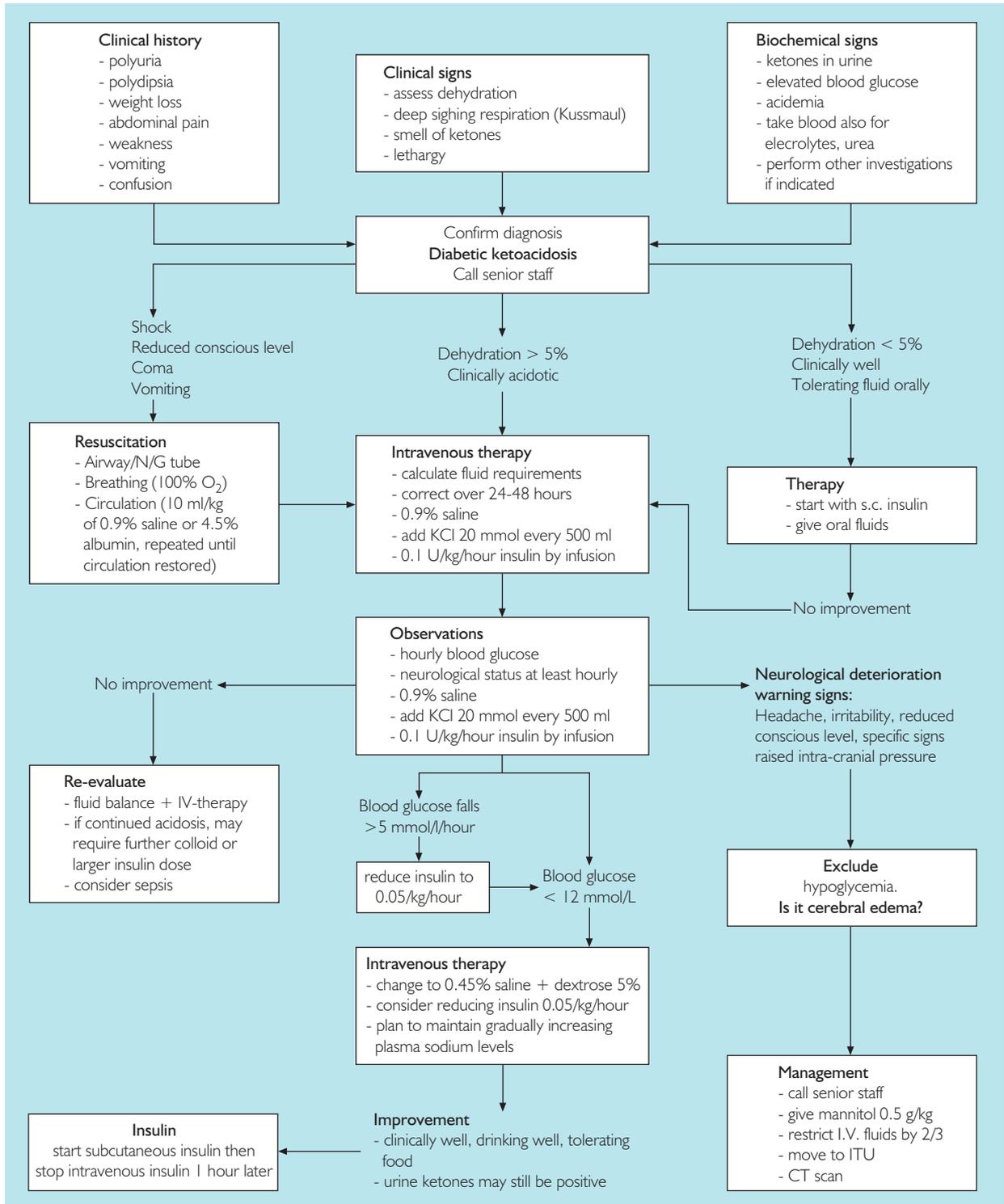


Fig. 10.15 Algorithm for the management of diabetic ketoacidosis. Notes and algorithm designed for Diabetes UK © by Dr Julie Edge and a working party of the British Society for Paediatric Endocrinology and Diabetes including the author (J.W.). This information is reproduced with the kind permission of Diabetes UK, the charity for people with diabetes (www.diabetes.org.uk). Initially adapted by Diabetes UK and reproduced here from *Practical Algorithms in Pediatric Endocrinology*, ed. Z. Hochberg, Karger, Basel, 1999, with permission.

NOTES

These guidelines are recommended to be used for children who are

- more than 5% dehydrated and acidotic
- and/or vomiting.

No guidelines have been shown to eliminate the risk of cerebral edema, but the principles outlined in these guidelines are believed to be as safe as possible in the light of current research and clinical practice. Guidelines should not replace intelligent thought and should be tailored to meet the needs of each individual patient; junior medical staff should always be encouraged to contact a more senior member of the medical team as soon as DKA is suspected.

The algorithm should not be used in isolation, and the following notes are an essential adjunct.

Diagnosis

- This is usually not difficult, but the combination of hyperglycemia, acidosis and ketones must be found.
- Severe metabolic acidosis in the absence of hyperglycemia (or other obvious causes of acidosis such as renal failure) raises the possibility of lactic acidosis (including glycogen storage disease type I), alcoholic ketoacidosis, salicylate overdose, other inborn error of metabolism (propionic acidemia, methylmalonic acidemia) and sepsis (Gram negative).

Resuscitation

- There are theoretical reasons why colloid (such as 4.5% human albumin solution) may be preferable to saline in restoring circulating volume. However, in the light of recent concerns 0.9% saline is used more frequently. The choice should be left to individual units.

Dehydration

- To evaluate the degree of dehydration the usual clinical signs should be used, but over-estimation may occur; first signs appear at 3% and a capillary refill time of more than 3 seconds indicates 10% dehydration. Use a maximum of 10% dehydration for the initial calculations.

Coma on admission

- Always document conscious level in the notes, Glasgow Coma Score if depressed.
- True coma at admission is rare (less than 10%), but conscious level may be impaired at presentation.
- If the child presents with coma, other possible causes must be considered (DKA may have been precipitated secondarily).
- Very rarely cerebral edema may occur early in the disease, before any intravenous treatment has been given.

Nursing and Observations

- Consider early on whether the child should be nursed on the intensive treatment unit (ITU) (if shocked, very acidotic or very young, or ward staff stretched or inexperienced).
- Regular observations should be carried out from the start, and doctors informed of significant changes; neurologic observations may be required every half hour initially, and doctors should be informed of headache or behavior change promptly, even during the night, as these may indicate cerebral edema.

Fluid requirements

- The volume of fluid to be replaced is based on the deficit (degree of dehydration) plus the maintenance (basal 24-h requirement), given at a constant steady rate over the first 24 h; ongoing losses should be replaced if excessive and balance remains negative.
- The debate over the duration of fluid replacement (24, 36 or even 48 h) is still ongoing; rapid infusion of large volumes of fluids has been suggested but not proven as a risk factor for the development of cerebral edema. In general, 24 h is suggested as the rehydration period, but if the child is very young or the blood glucose level very high, a longer duration may be appropriate.
- 0.9% saline is used at the start of intravenous therapy until the blood glucose level falls to around 12 mmol/L.
- Once the blood glucose level falls to 12 mmol/L, 0.45% saline is preferable to 0.18% saline, because there is some evidence that falling plasma sodium concentrations may be associated with cerebral edema.

Insulin dose

- 0.1 units/kg/h have been chosen as the standard insulin infusion rate. Some suggest using a lower dose (0.05 units/kg/h), particularly in younger children. There is no good evidence to support either regimen, but lower doses may be insufficient to switch off ketogenesis.
- If blood glucose concentration falls by more than 5 mmol/L/h, then the insulin dose may be reduced to 0.05 units/kg/h.
- **Do not** switch off the insulin infusion rate if the blood glucose falls: add more dextrose to the infusate – insulin is needed to reverse the ketosis.

continued on next page

Fig. 10.15 *continued*

Bicarbonate

- There is no experimental evidence to support the use of bicarbonate in the treatment of the metabolic acidosis in DKA.
- If acidosis persists, consider giving further colloid, increasing the dose of insulin (more glucose may need to be added to the fluids), or the possibility that the child is septic.

Cerebral edema

- This complication of DKA is almost exclusively a condition of childhood.
- The pathophysiology is still not completely understood.
- Usually occurs between 4 and 12 h from the start of treatment, but may be present at onset of DKA and can occur up to 24 h later.
- The clinical signs are variable: gradual deterioration and worsening of conscious level from admission, or more commonly a gradual general improvement followed by sudden neurologic deterioration.
- Requires urgent recognition and intervention; the treatment of choice is mannitol (0.5–1.0 g/kg; 2.5–5 mL/kg mannitol 20%), which should be given immediately there is neurologic deterioration.
- Headache may be a symptom; severe headache should also be treated with mannitol.
- Admit to ITU. Intubation and hyperventilation may be required. Computed tomography to rule out other diagnoses.



Fig. 10.16
Insulin resistance
and obesity.



Fig. 10.17 Acanthosis nigricans with insulin resistance.

abnormal receptor or post-receptor signaling mechanism and greatly increased insulin levels in the presence of usually moderate hyperglycemia. There is acanthosis, and females present more often than males with virilization, hirsutism, skin tags and oligomenorrhea (the HAIR-AN syndrome of hyperandrogenization, acrochordons, insulin resistance and acanthosis nigricans; **Fig. 10.18**). There is an increase in free insulin-like growth factor (IGF) 1 concentration, which may result in rapid late childhood growth with acromegaloid

features and very low sex hormone binding globulin (SHBG) levels, worsening the free testosterone index. In a specific phenotype of abnormal dentition, precocious puberty, abnormal skin and nails, hirsutism and pineal hyperplasia, there are also insulin receptor abnormalities (the Rabson–Mendenhall syndrome).

Insulin resistance is also seen in association with the Leprechaun syndrome (see **Figs 4.19 & 4.20**) and other congenital generalized lipodystrophies.

The possibility now exists of treating these forms of resistance due to abnormal insulin receptors with recombinant IGF-1, although availability is limited, and work is being performed to bypass the receptor by stimulating post-receptor signaling.

Diseases of the pancreas, such as pancreatitis, neoplasia, trauma (including surgery for hyperinsulinism; see Ch. 11) and stones may result in endocrine pancreatic insufficiency and diabetes. In cystic fibrosis the

Fig. 10.18

Acanthosis nigricans in severe insulin resistance (type A) leading to HAIR-AN syndrome (see also Figs 6.34 & 6.35).

**Fig. 10.19**

Congenital rubella may lead to later diabetes.



pancreatic fibrosis results in cystic fibrosis-related diabetes (CFRD) in about 10% of adolescents with the condition, although the incidence increases with increasing survival. Glucagon secretion is also affected, resulting in a tendency to hypoglycemia on treatment but also a lessening of the risk of ketosis. If undetected, the catabolism produced by incipient diabetes will cause a reduction in respiratory function and so CFRD should be prospectively screened for in all teenagers with cystic fibrosis. Sulfonylurea therapy or insulin should be instituted early to prevent catabolism and coupled

**Fig. 10.20** Ataxia telangiectasia.

with a high-calorie diet (with no restriction on intake of fat), designed to reverse any weight loss.

Hemochromatosis causes diabetes through iron overload, as does thalassemia in about 10% of cases. Cystinosis damages the pancreas (and thyroid) as a result of the intracellular accumulation of free cystine.

Endocrine abnormalities covered elsewhere in this book can result in glucose intolerance or frank diabetes. Gigantism, Cushing syndrome and thyrotoxicosis can all affect glucose metabolism. Iatrogenic Cushing syndrome, especially in the early phases of treatment of brain tumors and following bone marrow transplantation, can result in intermittent frank diabetes requiring insulin during each 'pulse' of therapy. Asparaginase has an additive toxic effect on the pancreas. Very rare tumors such as glucagon- and somatostatin-producing tumors of the pancreas, and occasionally pheochromocytomas, can all result in diabetes.

Drug- or chemical-induced diabetes and glucose intolerance may be seen with thiazide diuretics and diazoxide (which are used in the treatment of hyperinsulinism; see Ch. 11). Specific drugs such as pentamidine, dilantin, α -interferon, β -adrenergic agents and toxins in some foods can damage the pancreas.

Congenital infections such as rubella (**Fig. 10.19**) and cytomegalovirus may result in diabetes from an early age, and rare systemic infections such as with *Nocardia* can destroy the pancreas.

Immune-modulated diabetes is due to antibodies against the insulin receptor. Type B insulin resistance and 'stiff man syndrome' usually occur late in life, but in 60% of patients with ataxia telangiectasia (**Fig. 10.20**) there is glucose intolerance associated with anti-insulin receptor antibodies.

Syndromic associations of diabetes include the Klinefelter (Ch. 3), Ullrich-Turner and Down syndromes (Ch. 2), and a number of non-chromosomal

disorders. Insulin resistance may be a feature of several dysmorphic conditions associated with obesity, including the Bardet–Biedl, Alstrom and Prader–Willi syndromes (Ch. 5). Glucose intolerance is seen in many cases of dystrophia myotonica, and occasionally in Huntington’s disease. The DIDMOAD (or Wolfram) syndrome of diabetes insipidus, diabetes mellitus, optic atrophy (see Fig. 1.111) and deafness is a severe autosomal recessive disorder characterized by diabetes mellitus and optic atrophy in the first decade. Diabetes insipidus and deafness occur in the second decade, psychiatric and renal abnormalities in the third decade, and finally CNS degeneration with myoclonus and ataxia. About 25% have gastrointestinal dysmotility and 25% of males are hypogonadal. Death occurs between 25 and 50 years of age. It is a heterogeneous syndrome caused by mutations at two different sites on chromosome 4, and a mitochondrial form has also been described. Roger syndrome has a superficially similar presentation with early visual and eighth nerve abnormalities and diabetes, but no other CNS involvement. There may be an accompanying sideroblastic anemia. It is due to an autosomal recessive thiamine transporter defect; the diabetes and anemia respond to high doses of thiamine. Most kindreds have originated from Kashmir.

NEONATAL DIABETES

Transient neonatal diabetes is characterized by the early onset (<6 weeks) of glycosuria and wasting. The children are often small for gestational age and look alert and anxious (Figs 10.21 & 10.22). The blood sugar level is often markedly raised and ketosis is mild or absent. Thrombotic events may occur secondarily to the dehydration. The illness is of unknown etiology, and patients are antibody negative, although familial occurrence is described. Insulin and C-peptide levels are low and it is postulated that there may be ‘delayed maturation’ of the pancreas. Treatment is with insulin (although the infant may be very sensitive to this). The condition remits spontaneously after a few weeks or months, and rising C-peptide levels can be used as a clue to the timing of discontinuation of treatment. Later, permanent diabetes occurs in the second decade in many infants, suggesting the mechanism may be related to permanent abnormalities of beta-cell mass or function. Permanent diabetes may occur from the neonatal period, and can be differentiated from the transient form only in retrospect, unless there is complete pancreatic agenesis in which case exocrine pancreatic function is also abnormal. Isolated beta-cell aplasia may rarely occur. In DR3/4 and antibody-positive individuals, type 1 diabetes has been rarely described dating from the



Fig. 10.21 Neonatal diabetes, whole body view.



Fig. 10.22 Face of baby shown in Fig. 10.21.

neonatal period. The Wolcott–Rallison syndrome consists of neonatal diabetes mellitus and epiphyseal dysplasia due to a mutation of a translational factor.

TYPE 4 DIABETES

Type 4, gestational, diabetes occurring in 3–5% of pregnancies may represent the unmasking of glucose intolerance during prenatal care. Glucose homeostasis returns to normal post-partum, although the risk of subsequent type 2 diabetes is high.

TYPE 5 DIABETES

Type 5 diabetes (malnutrition related or tropical diabetes) is seen in adolescents and young adults who are thin and have a history of previous malnutrition

(see Ch. 4). They often require large amounts of insulin but are surprisingly ketosis free. They may be difficult to distinguish from patients with type 1 diabetes. Fibrocalculous pancreatic disease again often results in diabetes in young adult males with a history of past malnutrition and abdominal pain. It may be related to cyanide ingestion from foodstuffs such as cassava on a genetically susceptible background.

HISTORY AND EXAMINATION

- Family history of type 1 diabetes or autoimmune disease, of type 2 diabetes in a first-degree relative or of MODY.
- Polyuria, polydipsia = glycosuria, diabetes insipidus in DIDMOAD syndrome.
- Weight loss = type 1 diabetes, or autoimmune process in syndrome.
- Drug history, chemotherapy.
- Known cystic fibrosis, thalassemia, Down or Turner syndrome, etc.
- History of past malnutrition = possible tropical diabetes.
- Ethnic subgroup = predisposition to type 2 diabetes in Asians, Polynesians, etc. Roger syndrome in Kashmiris.
- Dehydration and ketosis = type 1 with DKA.
- Acanthosis = insulin resistance.
- Candidiasis, staphylococcal skin infection = poorly controlled diabetes.
- Retinal pigmentary changes, neurologic signs = mitochondrial abnormality.
- Deafness, optic atrophy = DIDMOAD or Roger syndrome.
- Diabetes insipidus, psychiatric features = DIDMOAD.
- Hirsutism, skin tags, acanthosis = HAIR-AN syndrome.
- Cushingoid appearance = Cushing syndrome.

WORK-UP

Most childhood diabetes will be type 1, and little diagnostic testing is required. If resources allow, it is useful to measure anti-islet cell, anti-GAD antibodies; other autoantibodies (including antithyroid and anti-gliadin antibodies) should be measured at diagnosis (then 4 yearly), in addition to true blood sugar and glycosylated hemoglobin levels (which gives an indication of length of prodromal phase). At follow-up glycosylated hemoglobin should be measured regularly and thyroid function checked 3–4 yearly if antibody positive.



Fig. 10.23 Imperforate anus in infant of a diabetic mother.

To differentiate between type 2 diabetes and the various forms of MODY, it is usual to genotype the individual, looking for the known MODY mutations or confirm the same genotype as in an affected relative (see Appendix). Insulin levels (or the insulin : glucose ratio) will be moderately raised in type 2 diabetes, but massively so in insulin receptor defects.

The two common mutations for DIDMOAD (4p and 4q) are known (although a mitochondrial form has also been described), and Roger syndrome (1q) may be analyzed.

THE INFANT OF A DIABETIC MOTHER

It is important to educate potential mothers with any form of diabetes about the need for planned conception at a time of assiduous control. Periconceptional diabetes clinic attendance can improve fetal malformation rates from 10% to 2%. The teratogenic effects of maternal diabetes have their effects in the first 8 weeks of pregnancy and are related to the glycosylated hemoglobin levels in the first trimester. The mechanisms for the effects on the developing fetus are ill understood. The congenital abnormalities seen include:

- Caudal regression and recto-anal atresia (**Fig. 10.23**).
- Spina bifida, hydrocephalus and anencephaly.
- Situs inversus, transposition of the great arteries, ventricular septal defects.
- Renal abnormalities.

Later control influences birth size (see Ch. 3) and hence complications of macrosomia such as shoulder dystocia, birth asphyxia and birth injury. The incidence of respiratory distress syndrome, neonatal hypoglycemia, jaundice and hypocalcemia is also related to fetal hyperinsulinism in the last trimester.

