Adult spontaneous hypoglycaemia

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Spontaneous hypoglycaemia is not a diagnosis, but a manifestation of a disease process. It is important to recognize spontaneous hypoglycaemia, as treatment may be preventative or curative. It is equally important to avoid mislabelling healthy individuals as having hypoglycaemia as this may have a negative impact on the quality of life and use of scarce health-care resources.

Although hypoglycaemia has many causes, in practice it is usually a result of over-treatment of diabetic patients with insulin or oral hypoglycaemic drugs. This article reviews the clinical investigation of spontaneous (non-diabetic) hypoglycaemia in adults which, although uncommon, is important because preventative or curative therapy is often available.

INVESTIGATION OF HYPOGLYCAEMIA

Investigation of hypoglycaemia and suspected hypoglycaemia involves:

- A high index of suspicion
- Confirmation or exclusion of hypoglycaemia
- Elucidation of the cause of confirmed hypoglycaemia. (Marks, 1992; Service, 1993; Marks and Teale, 1996; Service, 1999a, 1999b; Gama et al, 2003; Service, 2004).

I) HIGH INDEX OF SUSPICION

Spontaneous hypoglycaemia should be considered in anyone who presents with an episodic subacute neuroglycopaenia, even if there may be an alternative explanation for the symptoms.

Clinical characteristics of neuroglycopaenia

The clinical features of hypoglycaemia are mediated through altered brain activity and are termed neuroglycopaenia (Marks, 1992). There are three neuroglycopaenic syndromes: acute, subacute and chronic neuroglycopaenia. Spontaneous hypoglycaemia commonly presents with subacute neuroglycopaenia, which is characterized by episodic disorientation, somnolence, slurring of speech, personality changes, amnesia and loss of consciousness. Not infrequently, consciousness may be lost without any premonitory symptoms and is analogous to hypoglycaemic unawareness seen in patients with diabetes mellitus.

Acute neuroglycopaenia, associated with iatrogenic hypoglycaemia, is characterized by sweating, anxiety, tremor, palpitations, tachycardia, pallor, hunger and paraesthesiae. Clinical features common to both acute and subacute neuroglycopaenia include transient hemiplegia, strabismus, hypothermia, hyperthermia, convulsions and automatism. Untreated, these may progress to coma and even death from cerebral oedema.

Chronic neuroglycopaenia, virtually confined to patients with insulinoma or diabetic patients over-treated with insulin, is extremely rare and presents with insidious progressive mental illness resembling chronic psychiatric disorders.

II) CONFIRMATION OR EXCLUSION OF HYPOGLYCAEMIA

Definition of hypoglycaemia

Although arbitrary, the generally accepted definition of hypoglycaemia is an arterial plasma glucose concentration of 3.0 mmol/litre or less (Marks and Teale, 1996). This value has therefore been used in this article.

Homeostatic mechanisms, however, are activated with suppression of endogenous insulin secretion when plasma glucose falls to about 4.0 mmol/litre and release of counter-regulatory hormones when plasma glucose falls to approximately 3.7 mmol/litre (Bolli and Fanelli, 1999; Cryer, 1999). This suggests that hypoglycaemia should only be definitively excluded when plasma glucose is 4.0 mmol/litre or greater.

DIAGNOSTIC CRITERIA FOR HYPOGLYCAEMIA: WHIPPLE'S TRIAD

Neuroglycopaenic symptoms are non-specific. Acute and subacute neuroglycopaenia can, there-

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fore, only be confidently confirmed when Whipple's triad (Gama et al, 2003) is fulfilled, i.e. neuroglycopaenic symptoms, a low blood glucose and symptoms relieved by raising blood glucose to or above normal.

CLINICAL APPROACH TO SUSPECTED HYPOGLYCAEMIA

Blood samples must be collected when symptomatic, firstly to confirm or exclude hypoglycaemia and secondly, if confirmed, it offers an ideal opportunity to uncover its underlying cause. During symptoms, a plasma venous glucose of 4.0 mmol/litre or greater excludes hypoglycaemia, whereas a value of 3.0 mmol/litre or less confirms hypoglycaemia and further investigation is mandatory. Intermediate values may require further investigation but this will depend on the level of clinical suspicion.

Patients are usually asymptomatic with unhelpful blood glucose values during consultation in the outpatient clinic. The options are then either to obtain a blood sample during symptoms for laboratory measurement of glucose or try to provoke a hypoglycaemic attack.

Obtaining a blood sample during symptoms entails training the patient, relative or friend to collect a capillary blood sample into a suitable capillary tube, or onto specially prepared filter paper for later laboratory blood glucose measurement (Marks and Teale, 2001). If hypoglycaemia is confirmed, further investigation is obligatory.

Provocation of hypoglycaemia involves fasting, with or without exercise, when fasting hypoglycaemia is suspected, or giving a mixed meal when reactive hypoglycaemia is suspected. Other provocative tests are of limited value in the initial investigation of hypoglycaemia because of poor diagnostic specificity and sensitivity. The L-leucine test, intravenous glucagon test, intravenous tolbutamide test (not available in the UK) and selective arterial pancreatic calcium stimulation test may have a limited role in the differential diagnosis of hypoglycaemia, but not in its initial investigation (Service 1993; Gama et al, 2003).

PROVOCATION TESTS

Overnight Fast

Most patients with episodic spontaneous hypoglycaemia will have at least one overnight fasting (18 hours) plasma glucose concentration of <2.5 mmol/litre, when measured on three separate occasions (Marks, 1992). The hypoglycaemic episodes may appear asymptomatic; however, if specifically sought, they can often be shown to be associated with mild impairment of cognitive function.

PROLONGED FAST

The 72-hour fast remains the gold standard for investigating fasting hypoglycaemia (Service, 1999b). It has been advocated that the 48-hour fast is as diagnostically efficient as, and should replace, the 72-hour fast (Hirsberg et al, 2000), although this has been disputed (Service and Natt, 2000). A prolonged fast should be reserved for those patients in whom hypoglycaemia remains a strong possibility but have not experienced a documented spontaneous or provoked hypoglycaemic episode.

The fast is conducted in hospital under medical supervision. During the fast the patient is allowed to drink non-caloric and caffeine-free beverages and encouraged to be as ambulant as possible. Blood samples are collected every 6 hours until plasma glucose falls to 3.5 mmol/litre. The sampling interval is then reduced to every 1–2 hours and the patient regularly assessed for neuroglycopaenia. Blood samples are immediately analysed for plasma glucose and serum stored frozen for later measurement, if required, of pancreatic B-cell products, insulin antibodies, beta-hydroxybutyrate (ß-OHB) and appropriate drug screen. The fast is terminated, after appropriate specimen collection, when plasma glucose falls below 2.5 mmol/litre and the patient has neuroglycopaenic symptoms. In the absence of symptoms and hypoglycaemia the test is terminated at 72 hours. The patient is fed at the end of the test.

A few healthy individuals, usually young women, may have plasma glucose concentrations in the range of 2.5 mmol/litre or less following prolonged fasting (Service, 1999b). They may be misdiagnosed as having hypoinsulinaemic hypoglycaemia, however, they do not develop neuroglycopaenia.

MIXED MEAL TEST

The mixed meal test is used to investigate patients with post-prandial neuroglycopaenic symptoms for the possibility of reactive hypoglycaemia (Marks, 1992; Service, 1999a, 1999b; Brun et al, 2000). Capillary blood samples are collected before and at 30-minute intervals for 6 hours after ingestion of a carbohydrate-rich mixed meal. There is no standardized meal, but it should be similar to that which caused symptoms during everyday life. The test is considered positive if the patient develops neuroglycopaenia in the presence of a capillary plasma glucose level of 3.0 mmol/litre or less (Service, 1999b). Venous blood should not be used as it may give false positive results since post-prandial glucose concentrations in venous samples may be up to

2 mmol/litre lower than in corresponding capillary samples (Marks and Teale, 1996).

The prolonged (5-hour) 75 g glucose tolerance test is not recommended in the investigation of reactive hypoglycaemia. This is because a large number of healthy subjects will have a false positive result, especially if venous blood samples are collected (Yager and Young, 1974; Johnson et al, 1980; Lefebvre et al, 1988).

GLUCOSE SAMPLE COLLECTION AND ANALYSIS

The type of blood sample and its site of collection influences glucose results. Whole blood glucose concentrations may be 15% lower compared with plasma concentrations (Marshall and Bangert, 2004). In the fasting state, arterial and venous glucose concentrations are very similar. As a result of tissue uptake of glucose, however, post-prandial venous blood glucose concentrations may be up to 2 mmol/litre lower than in corresponding arterial samples (Marks and Teale, 1996). Arterial blood glucose concentrations determine the development of neuroglycopaenia, and injudicious collection of post-prandial venous samples may, therefore, result in pseudohypoglycaemia. Arterial blood sampling is, however, impractical. Free-flowing capillary blood is suitable as its glucose concentrations approximate very closely to arterial blood. Stagnant capillary blood, however, results in significant underestimation of arterial glucose concentrations.

Hypoglycaemia should be documented by an accredited laboratory glucose measurement. Glucose meters, especially visually read glucose test strips, are unsuitable for the diagnosis of spontaneous hypoglycaemia (Burden et al, 1998; Gama et al, 2000). Glucose meters may, however, be useful in the emergency clinical environment as a guide to the immediate need for further blood collection (for confirmation and further investigation of hypoglycaemia), rapidly followed by resuscitation with glucose. In addition, caution should be exercised using the Yellow Springs Instrument (YSI) in defining hypoglycaemia since its negatively biased results (Twomey, 2004) may misclassify normoglycaemic individuals as being hypoglycaemic.

III) ELUCIDATING THE AETIOLOGY OF DOCUMENTED HYPOGLYCAEMIA

Particular attention should be paid to drug and alcohol history (Hart and Frier, 1998; Marks and Teale, 1999; Service, 1999a), especially in the presence of co-existent disease or exercise or both. In the ill, hospitalized patient, it is usually sufficient to recognize the underlying disease and its association with hypoglycaemia, and take preventative measures without recourse to further investigation.

In the apparently healthy individual, an algorithm for the differential diagnosis of documented hypoglycaemia is given, which will elucidate most causes of hypoglycaemia (*Figure 1*). It is important that initial laboratory investigations are carried out in hypoglycaemic samples. Samples following the administration of glucose are valueless and may be misleading.

TESTS USED TO ELUCIDATE THE CAUSE OF HYPOGLYCAEMIA

Insulin

Specific insulin assays have largely replaced non-specific insulin assays (also termed immunoreactive insulin or IRI), which measured not only insulin, but also detected proinsulin and its partially processed fragments (Clark, 1999). Some of the very specific insulin assays may fail to detect new synthetic insulins, older animal insulins and insulinomas exclusively secreting proinsulin (Clark, 1999; Marks, 2001; Piovesian et al, 2003).

C-peptide

C-peptide is co-secreted with insulin from the pancreas in equimolar concentrations. Since insulin has a shorter half-life than C-peptide, and is extracted from the portal circulation by the liver, peripheral C-peptide concentrations are several fold higher than those of insulin. Its major clinical use is in the detection of exogenous insulin-induced hypoglycaemia (Clark, 1999). C-peptide is cleared by the kidneys, and is therefore elevated in renal impairment. This may cause difficulties in the investigation of hypoglycaemia in patients with renal disease (Basu et al, 2002).

Proinsulin

Proinsulin normally represents less than 10% of circulating IRI. The proinsulin assay is used to identify insulinomas exclusively secreting proinsulin (Clark, 1999; Piovesian et al, 2003).

Ketones (ß-hydroxybutyrate)

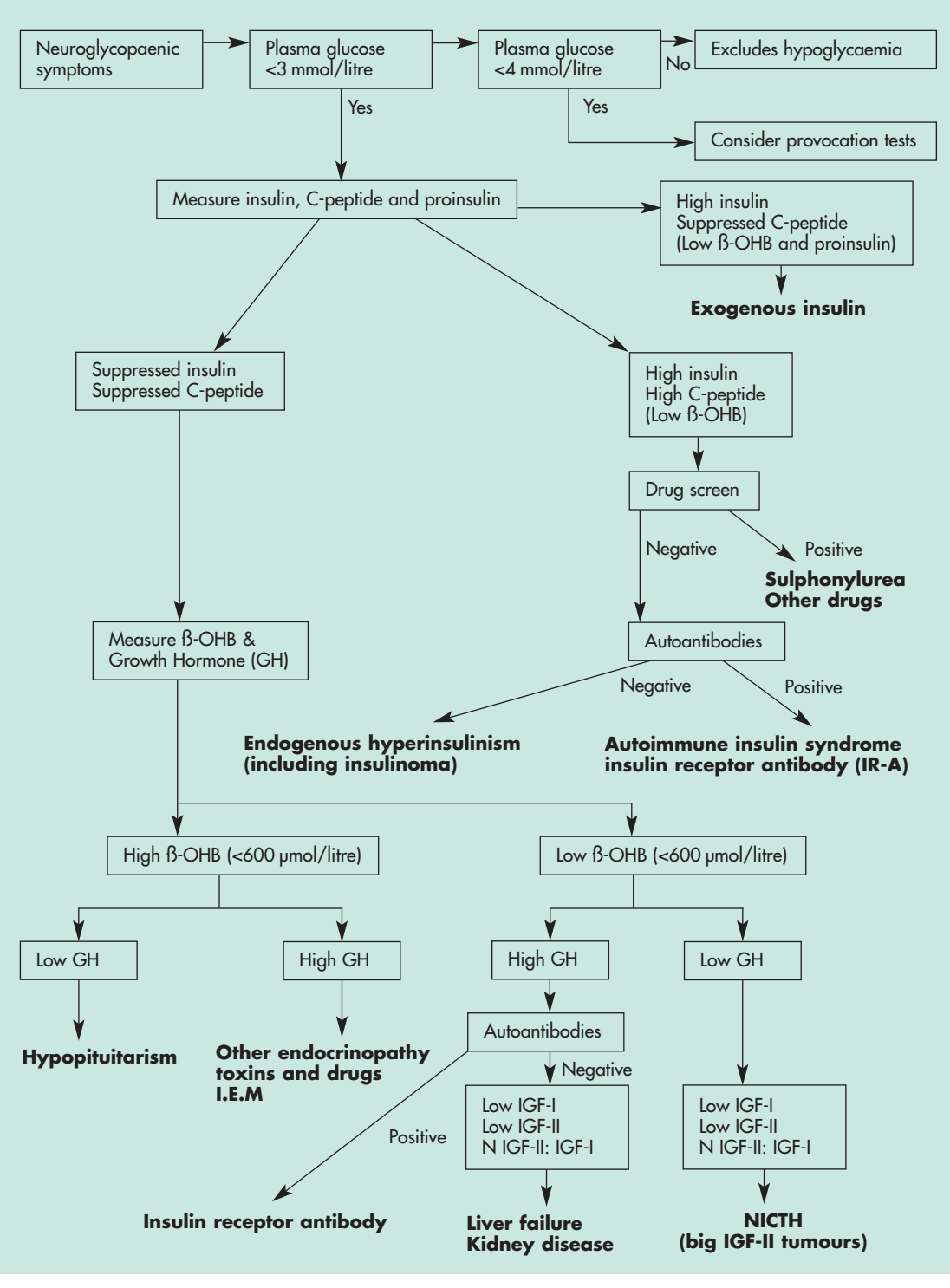
During hypoglycaemia, fat is mobilized to liberate non-esterified fatty acids, which are then used by the liver to produce ketones. Hypoglycaemia is therefore usually associated with moderate to marked ketonaemia, unless ketosis is suppressed (<600 µmol/litre) by inappropriate insulin or insulin-like activity, or failure to produce ketones because of liver failure or absence of fat stores (severe anorexia nervosa and starvation) (Marks, 1992).

Insulin antibodies and insulin receptor antibodies.

Insulin antibodies may develop in response to exogenous insulin, but also occur in patients never exposed to exogenous insulin. They may cause reactive hypoglycaemia described as the autoimmune insulin syndrome (AIS) (Redmon and Nutall, 1999). Insulin antibodies are considered the *sine qua non* for the diagnosis of AIS.

Insulin receptor antibodies (IR-A), depending on mode and site of action, may cause either hyperglycaemia or, very rarely, refractory hypoglycaemia (Redmon and Nutall, 1999). The diagnosis of IR-A mediated hypoglycaemia requires

Figure 1. Algorithm for the differential diagnosis of hypoglycaemia. ß-OHB = ß-hydroxybutyrate, I.E.M = Inborn errors of metabolism, IGF-I = Insuln-like growth factor-I, IGF-II = Insuln-like growth factor-II, NICTH = Non-islet cell tumor hypoglycaemia.



demonstration IR-A in the serum (Redmon and Nutall, 1999).

AETIOLOGY OF HYPOGLYCAEMIA

Hyperinsulinaemic hypoglycaemia

The hallmark of hyperinsulinaemic hypoglycaemia is inappropriate insulin secretion – not necessarily excessively high peripheral insulin levels – in the presence of hypoglycaemia. Although rare, the most common cause of endogenous hyperinsulinaemic hypoglycaemia is insulinoma. Insulinomas are pancreatic B-cell tumours characterized by inappropriately high insulin and/or proinsulin, high C-peptide and low ß-OHB serum levels. A pure proinsulinoma may be mistaken for hypoinsulinaemic hypoglycaemia if very specific insulin assays are used, but are easily identified by the measurement of plasma proinsulin (Clark 1999; Piovesian et al, 2003).

Serum calcium should be measured in patients with insulinoma, because insulinoma may be a feature of type 1 multiple endocrine neoplasia. Selective pancreatic arterial calcium stimulation, endoscopic ultrasound and intra-operative ultrasound may be of value in localization of insulinoma (Grant, 1999), while other imaging techniques have poor diagnostic sensitivity and specificity and, therefore, are unreliable and may be misleading. The successful removal of an insulinoma is dependent on surgical experience and expertise.

Other causes of hyperinsulinaemic hypoglycaemia, including factitious hypoglycaemia and autoimmune hypoglycaemia, should be excluded before making a diagnosis of insulinoma. This is especially important for factitious hypoglycaemia induced by pancreatic secretagogues, which produce an identical clinical and biochemical picture to insulinoma (Marks and Teale 1999; Hirshberg et al, 2001; Kwong and Teale, 2002). Exclusion by showing an absence of these compounds in blood and urine at the time of hypoglycaemia is essential to prevent unnecessary laparotomy (Perros et al, 1997). Although rare, it has also been recommended that insulin antibodies be sought in patients with documented hypoglycaemia (Service, 2004), as this may avoid unnecessary pancreatic surgery (Sklenar et al, 1987).

Hypoglycaemia resulting from exogenous insulin administration is easily distinguished from that resulting from endogenous hyperinsulinism by inappropriately high insulin levels in the presence of low or suppressed C-peptide levels. Very rarely, this picture may be produced by insulinomas exclusively secreting proinsulin if non-specific insulin assays are used and by IR-A mediated hypoglycaemia.

Proinsulinomas can be identified by hyperproinsulinaemia. Diagnosis of IR-A mediated hypoglycaemia requires demonstration of IR-A in the serum, and should be considered in patients with autoimmune disease and some varieties of neoplastic disease (Redmon and Nutall, 1999). Importantly, some very specific insulin immunoassays fail to detect the new synthetic insulins and animal insulins (Clark, 1999), and therefore may fail to identify their factitious or felonious use. The diagnosis of reactive hypoglycaemia is usually obvious from its typical clinical history and, if required, can be confirmed with a mixed test meal.

HYPOINSULINAEMIC HYPOGLYCAEMIA

Hypoinsulinaemic hypoglycaemia is characterized by suppressed serum insulin (and proinsulin) levels in the presence of hypoglycaemia. This is accompanied by low or suppressed serum C-peptide levels, except in kidney disease because of decreased renal clearance of C-peptide.

Rarely, extra-pancreatic tumours may present with spontaneous hypoglycaemia and is termed non-islet cell tumour hypoglycaemia (NICTH) (Marks and Teale, 1998). NICTH most commonly results from excessive tumour secretion of abnormal insulin-like growth factor-II (big IGF-II), but also includes other very rare causes of hypoglycaemia as a result of IR-A, insulin-binding monoclonal gammopathy, or as a result of tissue destruction by tumour, causing major organ failure or endocrine disease (Marks and Teale, 1998).

The insulin-like activity of big IGF-II leads to hypoglycaemia with consequent suppression of B-cell secretion, lipolysis and ketogenesis. Feedback of big IGF-II on the hypothalamic-pituitary axis suppresses growth hormone (GH) secretion with subsequent lowering of GH dependent IGF-I and IGF binding proteins secreted by the liver. Tumours secreting big IGF-II are, therefore, characterized by an increased total IGF-II:IGF-I ratio, suppressed insulin and C-peptide, and inappropriately low GH and ß-OHB levels.

Other causes of hypoinsulinaemic hypoglycaemia (*Table 1*) are usually clinically obvious from the history, clinical examination and laboratory investigations. Endocrin-opathies (particularly Addison's disease and hypopituitarism) may, however, be missed unless specifically sought. Measurement of counter-regulatory hormones in hypoglycaemic samples may give lower than expected values because of adaptation to chronic neuroglycopaenia and may erroneously suggest endocrine deficiencies. To avoid false positive mis-diagnoses, appropriate stimu-

TABLE 1.
Common causes of adult spontaneous hypoglycaemia

FASTING (POST-ABSORPTIVE) HYPOGLYCAEMIA

i) Hyperinsulinaemic hypoglycaemia

Pancreatic
Insulinoma
Nesiodioblastosis

Drug-induced
Insulin
Pancreatic secretagogues
Thiazolidinediones
Quinine
Salicylates
Disopyramide
Pentamidine
Many Others

Autoimmune hypoglycaemia
Autoimmune insulin syndrome (mimics fasting hypoglycaemia)
Insulin receptor antibodies (depending on site and mode of action)
Islet-cell stimulating antibodies

Miscellaneous
Sepsis including malaria and human immunodeficiency virus
Discontinuation of total parenteral nutrition

ii) Hypoinsulinaemic hypoglycaemia
Non-islet cell tumour hypoglycaemia
IGF-II secreting tumours, e.g. mesenchymal tumours, haemangiopericytomas, carcinomas of the liver, stomach and adrenals)
Lymphoma, myeloma and leukaemias
Metastatic cancer

Drug-induced
Beta-blockers

Dietary toxins
Alcohol
Unripe ackee nuts

Organ failure
Severe liver disease
End-stage renal disease and renal dialysis
Congestive cardiac failure
Acute respiratory failure

Endocrine disease
Generalized or selective hypopituitarism and hypothalamic insufficiency
Adrenal failure and cortisol resistance
Hypothyroidism

Autoimmune
Insulin receptor antibodies (depending on site and mode of action)

Inborn errors of metabolism
Glycogen storage disease
Carnitine deficiency
Disorders of gluconeogenesis
Disorders of mitochondrial ß-oxidation

Others
Sepsis
Starvation including anorexia nervosa
Severe excessive exercise

iii) Miscellaneous (mechanisms not clarified)
Sepsis
Drugs

REACTIVE (ABSORTIVE) HYPOGLYCAEMIA

Post-gastric surgery
Alcohol
Idiopathic reactive hypoglycaemia
Autoimmune insulin syndrome
Inborn errors of metabolism: Hereditary fructose intolerance
Galactosaemia
Non-insulinoma pancreatogenic hypoglycaemia
Postoperative removal of phaeochromocytoma
All causes of fasting hypoglycaemia may be associated with reactive hypoglycaemia.

lation tests may be needed to confirm an endocrinopathy.

REACTIVE HYPOGLYCAEMIA

Reactive hypoglycaemia occurs only in response to ingestion of a meal and generally occurs 2–4 hours after a meal. Reactive hypoglycaemia is relatively common after major gastric surgery and is also termed the late dumping syndrome. It is otherwise rare, but may be a result of AIS, alcohol, non-insulinoma pancreatogenic hypoglycaemia (NIPH) and early diabetes mellitus or idiopathic reactive hypoglycaemia.

AIS should be considered in patients with autoimmune disease or previous exposure to sulphydryl-containing drugs, who present with hypoglycaemia and inappropriately high insulin and incompletely suppressed C-peptide levels with disproportionately high insulin: C-peptide molar ratio (Redmon and Nutall, 1999). In AIS, insulin released post-prandially binds to the insulin antibody initially resulting in hyperglycaemia but then, as insulin is released from the insulin antibody, hypoglycaemia ensues. Insulin antibodies considered essential for the diagnosis of AIS may, however, also be detected in non-hypoglycaemic individuals (Redmon and Nutall, 1999). Occasionally the post-prandial hypoglycaemia in AIS may be delayed and appear to present with fasting hypoglycaemia.

After exclusion of insulinoma, islet cell hyperfunction in NIPH can be demonstrated by a two- to threefold increase in hepatic venous insulin during a pancreatic artery calcium stimulation test (Service, 1999b).

All causes of fasting hypoglycaemia may be associated, and very rarely present, with reactive hypoglycaemia. Idiopathic reactive hypoglycaemia may, therefore, only be diagnosed after exclusion of fasting hypoglycaemia.

CONCLUSIONS

Hypoglycaemia may occur as an epiphenomenon in many serious diseases. It is sufficient to recognize the disease's association with hypoglycaemia and then take appropriate action to prevent its recurrence.

In the apparently healthy individual, the diagnosis of a hypoglycaemic disorder requires a high index of suspicion, careful clinical assessment and methodical laboratory evaluation. Appropriate laboratory and subsequent radiological investigation will identify most causes of adult spontaneous hypoglycaemia. HM

Conflict of interest: none

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KEY POINTS

Potential pitfalls in the investigation of suspected hypoglycaemia:

- Inabilty to recognize subacute neuroglycopaenia as a feature of spontaneous hypoglycaemia.
- Mislabelling healthy individuals as 'hypoglycaemic' resulting in the 'worried well syndrome'.
- Failure to confirm or refute hypoglycaemia during symptoms.
- nappropriate use of glucose meters and visual glucose strips to document hypoglycaemia.
- Failure to provide hypoglycaemic samples in which to measure pancreatic hormones, counter-regulatory hormones and non-glucose substrates.
- Continued use of obsolete investigations, such as the prolonged oral glucose tolerance test.
- Laboratory failure to recognize limitations of their assays.
- Failure to exclude factitious and autoimmune hypoglycaemia as the cause of spontaneous hypoglycaemia.