Clinical Endocrinology

Spontaneous Hypoglycaemia

VINCENT MARKS

British Medical Journal, 1972, 1, 430-432

Spontaneous hypoglycaemia may be due to dysfunction of the endocrine glands, but more often it results from breakdown of the metabolic processes regulating glucose homoeostasis. All degrees of hypoglycaemia may be encountered—from an isolated, solitary, and temporary episode to a profound, constant, and virtually unrelievable hypoglycaemia. The correlation between the extent of hypoglycaemia and the nature and severity of the symptoms it produces in the nervous system is poor, and for this reason the various conditions are grouped under the heading of "neuroglycopenia." To establish that a patient's symptoms are due to neuroglycopenia it is necessary to show, firstly, that while he has symptoms the patient is hypoglycaemic, and, secondly, that the symptoms are relieved by intravenous glucose, but not by intravenous saline.

Symptoms

The symptoms of hypoglycaemia are numerous and diverse, and are independent of its aetiology except that they vary with age, rapidity of onset of the condition, and the body's adaptation to it.

In adults three distinct, but not mutually exclusive, syndromes are discernible. Acute neuroglycopenia is characterized by a vague sense of ill health, anxiety, panic, feelings of unnaturalness, and detachment from the environment. These symptoms are accompanied by palpitations, restlessness, nausea, or hunger. Objectively there is tachycardia, facial flushing, sweating, unsteady gait, and abnormal, often truculent, behaviour which may progress until there are alterations in consciousness and even coma.

In subacute neuroglycopenia features of autonomic nervous over-activity are absent. Instead there is a gradually developing sense of lethargy and somnolence associated with a reduction of spontaneous activity, conversation, and movement. Behaviour patterns resembling mild to severe alcoholic intoxication may develop and habitual tasks are poorly performed. The patient may become stuporose or even frankly comatose though spontaneous recovery is usual.

Because subjective symptoms are comparatively slight for the degree of functional impairment the patient often lacks insight into his disease. This not only delays his seeking medical advice but makes him an unreliable historian. For this reason when subacute or chronic neuroglycopenia is suspected an independent history should always be obtained from a close relative or friend.

Transient diplopia and strabismus are common in acute and subacute neuroglycopenia but, like all other signs and symptoms associated with these syndromes, both are rapidly and completely reversed by food. In adults hypoglycaemia may cause a transient hemiparesis but only rarely does it cause true epileptic convulsions, though these are common in the newborn and in older children.

There is nothing characteristic about neuroglycopenic coma except a low blood glucose concentration, though hypothermia may provide a clue to its nature. The possibility that hypoglycaemia is the cause of coma should always be checked by direct measurement of the blood glucose concentration at the bedside using Dextrostix.

Chronic neuroglycopenia is rarer than the other two syndromes and is characterized by an insidious change in personality, defective memory, abnormal or psychotic behaviour —often with paranoid features—and mental deterioration resembling presenile dementia; acute neuroglycopenic episodes may be entirely absent.

The predominantly "functional" nature of neuroglycopenic symptoms of all types accounts for the frequency with which patients suffering from hypoglycaemia are referred in the first instance to psychiatric and neurological, rather than to endocrine clinics.

Diagnosis and Differential Diagnosis

A diagnosis of hypoglycaemia can be made *only* by measuring the blood glucose concentration and should never be made on clinical grounds alone, however convincing the history and "physical" findings. Unfortunately this advice is not universally accepted and patients with vague symptoms are often labelled, without adequate proof, as suffering from hypoglycaemia and elaborate but ineffectual therapeutic regimens are started.

The only definitive diagnostic procedure for hypoglycaemia is the finding of a low blood glucose concentration in a properly preserved sample of blood collected during symptoms. If, as sometimes happens, this is a solitary or isolated episode, the opportunity to make a correct diagnosis may never recur. Neuroglycopenic effects on the nervous system are confirmed by observing clinical recovery produced by intravenous glucose, *after* blood has been collected for glucose measurement. Unfortunately recovery produced by glucose is not by itself proof that symptoms are neuroglycopenic; they may be hysterical, in which case the therapeutic effect of intravenous saline is remarkable.

Not all methods for measuring blood glucose concentration are equally reliable and knowledge of the analytical method used is essential if the result is to be interpreted correctly. With the specific techniques now available hypoglycaemia should be diagnosed only when the blood glucose concentration is less than 40 mg/100 ml or plasma glucose concentration less than 45 mg/100 ml.

Because neuroglycopenia is more often episodic than constant, it is seldom present when the patient consults his doctor. It is often possible, however, on the basis of the clinical history, to suspect hypoglycaemia and initiate investigations

Department of Clinical Biochemistry, University of Surrey, Guildford
VINCENT MARKS, D.M., F.R.C.P.ED., Professor

to prove this. Apart from measuring blood glucose concentration during a symptomatic episode there is no "best test" for spontaneous hypoglycaemia. The most appropriate test in any given patient is determined by the likely aetiology of the suspected hypoglycaemia. Before investigations are initiated a provisional differential diagnosis must be made on the basis of the clinical history and physical examination.

Over 100 diseases can produce spontaneous hypoglycaemia but for most practical purposes they can be classified into (a) conditions in which fasting provokes hypoglycaemia and (b) conditions in which hypoglycaemia develops only after exogenous stimulation.

Fasting Hypoglycaemias

INSULINOMA

Insulin-secreting tumours of the pancreas are not rare, though they are less common than parathyroid adenomas. The average large district general hospital probably admits one new case per year. In about 85-90% of cases the tumour is solitary and benign and usually does not exceed 1 cm in diameter. In about 10% to 15% of cases the tumour has metastasized by the time the patient is seen and in a tiny percentage of cases there is a generalized adenomatous enlargement of the islets of Langerhans. A small but important proportion of patients with insulinoma have polyglandular disease.

The patient is seldom seen for the first time while he is actually neuroglycopenic. More often he arrives asymptomatic, and somewhat reluctantly, in the doctor's surgery. Typically the history is one of increasingly frequent attacks of subacute neuroglycopenia. Classically these are said to occur before breakfast, but in my experience the first few attacks usually occur about 11·30 in the morning. Difficulty in waking normally is common in young people.

There is often a history of similar episodes in the past, sometimes several years earlier, which cleared up spontaneously. Patients rarely associate the act of eating with prevention or abortion of attacks, though the association can often be elicited by a carefully taken and corroborated history. Gain in weight is unusual unless the patient has been advised, wrongly, to eat or take glucose. Hunger is not a feature of the disease. Between neuroglycopenic episodes the patient is "perfectly well". There are no physical signs of ill health, and this probably explains why most patients are first diagnosed as suffering either from a functional psychiatric disorder, usually hysteria or depression, or from neurological disease.

Insulinomata are not responsive to normal homoeostatic control and cause hypoglycaemia by continuing to secrete insulin when there is very little demand for it. The total amount of insulin secreted may not be excessive. In most cases the diagnosis is not difficult once the condition has been suspected. After fasting overnight for twelve to sixteen hours the blood glucose concentration is subnormal in over 90% of cases—provided it is measured by means of a specific and accurate method on three or more occasions. The fasting plasma insulin concentration after an overnight fast is almost invariably raised, or at least in the upper part of the so-called normal range, which is, of course, inappropriate when hypoglycaemia is also present. A "high" fasting plasma insulin in the absence of hypoglycaemia is not diagnostic of insulinoma.

Further Investigations

In a small proportion of cases more extensive investigation may be required. Both the L-leucine and intravenous glucagon tests are simple and harmless. Characteristically after both of these stimuli there is an early (5 minutes) exaggerated rise in plasma insulin level. With L-leucine this is accompanied by a fall in blood glucose; with glucagon there is a subnormal rise, followed by a fall, in blood glucose. The intravenous tolbutamide test is potentially dangerous. It should be reserved for use in cases where insulinoma is possible, but unlikely, and only when fasting blood glucose concentration is consistently normal.

The prolonged fast is seldom necessary to establish a diagnosis of spontaneous hypoglycaemia. Both oral and intravenous glucose tolerance tests give unpredictable results. All patients in whom a diagnosis of insulinoma is made should have parathyroid and pituitary function tests performed to exclude pluriglandular syndromes. Arteriography of the coeliac axis is helpful in about one-third of the patients in localizing an insulinoma within the pancreas. Treatment of insulinoma is surgical, but if the tumour cannot be removed —either because the patient refuses operation, the tumour cannot be found, or it has already metastasized—palliative treatment with diazoxide and chlorothiazide may be effective.

NON-ISLET CELL TUMOURS

Hypoglycaemia may occur as an unusual manifestation, sometimes as a presenting feature, of a large variety of non-endocrine tumours. The history may be indistinguishable from that of insulinoma, though on examination evidence of serious somatic illness is usually present. The condition cannot be distinguished with certainty from insulinoma by biochemical means without measuring the plasma insulin level. Fasting plasma insulin levels are low and the blood insulin response to various stimuli—such as glucagon, leucine, glucose and tolbutamide—is diminished.

ENDOCRINOPATHIES

Hypoglycaemia is sometimes the presenting, predominant, or only clinically obvious abnormality in patients with various endocrine diseases. Well-recognized causes, which can usually be readily diagnosed by appropriate tests once the condition is suspected, include partial or total panhypopituitarism, adrenocortical insufficiency, and selective deficiencies of growth hormone or ACTH. Treatment is that appropriate to the specific endocrine disease.

Deficiency of glucagon has very recently been established as a cause of spontaneous hypoglycaemia. At present the diagnosis of this is exceedingly difficult and depends on the demonstration of a failure of plasma pancreatic glucagon to rise in response to stimulation by intraveneous arginine, pancreozymin, and other stimuli to glucagon secretion.

Stimulative Hypoglycaemias

REACTIVE HYPOGLYCAEMIA

The ingestion of a lot of carbohydrate (especially when taken in the form of a rapidly assimilable sugar) is followed, in most normal people, first by a short-lived rise and then by a fall, in the blood glucose concentration. The latter is accompanied in a fair proportion of perfectly healthy normal individuals by symptoms and signs of acute hypoglycaemia. The fall in venous blood glucose concentration is sufficient, in 30-40% of cases, to satisfy the definition of hypoglycaemia. When there are changes in the blood glucose levels and symptoms occur during a prolonged oral glucose test in a patient with spontaneous symptoms which could be neuroglycopenic in origin, they may illogically be accepted as "confirming" a diagnosis of "functional" or essential reactive hypoglycaemia.

Characteristically the patient with reactive hypoglycaemia is a woman aged 30-40, who has had symptoms on and off for many years without progression either in frequency or severity. They are usually emotionally labile individuals whose com-

plaints are of weakness, faintness, nerviness, palpitations, anxiety, irritability, and inward trembling. Hunger, nausea, headache, vertigo, and tinnitus are common. Though they often complain of "blackouts", objective evidence of altered consciousness is rare. Symptoms commonly develop mid-morning and are often provoked or exacerbated by exercise.

In a very few patients, most of whom have chemical diabetes or have undergone gastric surgery, this syndrome is demonstrably due to reactive hypoglycaemia—that is, the patient is hypoglycaemic while having spontaneous symptoms. Unfortunately in most cases direct evidence that symptoms are due to hypoglycaemia is not obtained. Diagnosis is made on the basis of an oral glucose test, and this may obscure rather than illuminate the true nature of the patient's illness. The alternative diagnosis of "neurosis" also inadequately describes the aetiology of this well-delineated clinical syndrome, the exact nature and pathogenesis of which remain obscure.

The five-hour oral glucose test with blood glucose and plasma insulin measurements is useful for defining those patients with reactive hypoglycaemia due to early chemical diabetes who might benefit from a low carbohydrate diet.

ALCOHOL-INDUCED HYPOGLYCAEMIA

Alcohol-induced hypoglycaemia is due to inhibition of gluconeogenesis and is relatively commoner in children who have accidentally drunk alcohol, than in adults, who may or may not take alcohol regularly. When first seen the patient is usually comatose and often hypothermic. Apart from severe hypoglycaemia, the only abnormality is the presence of alcohol in the blood—usually at low concentration. The condition should be suspected in any individual in whom the symptoms of "alcoholic intoxication" are atypical or unduly prolonged. Vigorous treatment with intravenous glucose and hydrocortisone initially is essential as the illness has a high mortality.

DRUG-INDUCED HYPOGLYCAEMIA

Many therapeutic agents—including such commonly prescribed drugs as salicylates, paracetamol, and antihistamines—may produce hypoglycaemia in susceptible individuals, especially children. The diagnosis of hypoglycaemia is made by measuring the blood glucose concentration. Differential diagnosis is based on the history, physical findings, and presence of drug, or toxin, in the blood or urine.

Hypoglycaemia in Infants and Children

Infants and children may suffer from any of the varieties of hypoglycaemia that affect adults. In addition there are several conditions that are confined to childhood.

NEONATAL HYPOGLYCAEMIA

The full impact of neonatal hypoglycaemia on subsequent mental development and health has been appreciated only during the past ten years. The condition is diagnosed by demonstrating a blood glucose concentration of less than 20 mg/100 ml on two or more occasions during the first 72 hours of life. It is usually due to defective gluconeogenesis coupled with increased glucose utilization. Dysmature and babies born to mothers with toxaemia of pregnancy are particularly at risk. Glucose by mouth is usually ineffective in correcting the hypoglycaemia and treatment with intraveneous glucose, with or without intramuscular cortisone, is advisable even before symptoms develop.

A less sinister type of hypoglycaemia occurs during the first 12 hours of life in babies of diabetic mothers and is due to hyperinsulinaemia.

KETOTIC HYPOGLYCAEMIA

This is probably the commonest type of spontaneous hypoglycaemia in children between the ages of $1\frac{1}{2}$ and 10 years. Typically there is a history of infrequent episodes of subacute neuroglycopenia associated with nausea and vomiting, usually occurring in the morning after a longer than normal period without food, especially during intercurrent infection.

The child is hypoglycaemic and grossly ketotic while he has symptoms, but is perfectly well at other times. The diagnosis is confirmed by provoking hypoglycaemia by feeding a ketotic diet. The results of measuring the overnight fasting blood glucose level and the results of the glucagon, tolbutamide, and L-leucine tests are all normal. Treatment is by preventing ketosis by ensuring that regular meals are taken, especially during febrile illnesses when glucose supplements may be given.

INBORN ERRORS OF METABOLISM

Several inborn errors of metabolism may cause hypoglycaemia, but in many children with recurrent hypoglycaemia no cause is found. Differentiation of this idiopathic hypoglycaemia of childhood, which is not a single entity, from insulinoma may be difficult or impossible without laparotomy; and this is seldom justified. Fasting plasma insulin assays may be helpful. They are generally inappropriately high in children with insulinoma and subnormal in idiopathic hypoglycaemia. The blood insulin responses to glucagon, glucose, and tolbutamide are usually normal, or low, in children with idiopathic hypoglycaemia and also (for reasons that are far from clear) in children with insulinoma.

Treatment

The immediate aim of treatment of hypoglycaemia is to restore the blood sugar to normal levels, either by sugar by mouth, or in the unconscious patient by an intravenous glucose injection (50 ml of 50% w/v glucose over two minutes). A further 50 ml of 50% w/v glucose, together with 100 mg hydrocortisone, may be given if consciousness does not return within 10-20 minutes but excessive hyperglycaemia must be avoided. Intramuscular injection of 1 mg glucagon, which is generally effective in iatrogenic hypoglycaemia, is often ineffective in spontaneous hypoglycaemia. When, despite restoration of the blood sugar levels to normal, the patient remains unconscious after $\frac{1}{2}$ to 1 hour, an intravenous infusion of 200 ml of 10% mannitol may be helpful.

Though long-term treatment of spontaneous hypoglycaemia is that of the causative disorder, treatment with diazoxide, 5-20 mg/kg per day by mouth, especially if combined with chlorothiazide, is often effective in cases that are not amenable to specific therapy. Diazoxide is a non-diuretic benzothiadiazine chemically related to the thiazide diuretics. It produces hyperglycaemia by several mechanisms including inhibition of insulin secretion, and stimulation of glucagon secretion. Its use is indicated in idiopathic hypoglycaemic, hypoglycaemia from liver glycogen disease and that due to overdosage of hypoglycaemic sulphonylureas and in patients with a benign insulinoma or a malignant tumour who cannot be cured surgically. Diazoxide seldom benefits patients with "idiopathic" or "essential reactive hypoglycaemia" supporting the suggestion that hypoglycaemia by itself is not the major cause of the symptoms in this disorder.

Partially successful attempts to destroy metastatic insulin-secreting tumours, either by non-specific antitumour agents (such as cyclosphosphamide) or by selective pancreatotrophic or β-cytotrophic agents (such as tubercidin and streptozotocin) have been reported. These agents are experimental and potentially dangerous and should be used only when conservative measures have failed.