The Management of the Hypoglycemic Patient

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Organic hypoglycemia may be caused by an insulinoma. This is a rare tumor, multiple in about 10% and malignant in about 10% of cases. Multiplicity is particularly likely when insulinoma occurs as part of the MEN 1 syndrome. When a patient exhibits Whipple’s triad, synchronous blood sugar and insulin estimations must be made, and repeated during fasting. Diagnosis depends on the finding of inappropriately high insulin levels in the presence of low blood sugars. Many stimulatory tests are available but none are as reliable as prolonged starvation, and probably should be abandoned.

Measurement of proinsulin and C-peptide are of particular value in the diagnosis and in elimination of factitious hypoglycemia.

Preoperative localization is most useful and can be achieved in up to 90% of patients by skillful selective angiography. Percutaneous portal venous sampling has been used and is particularly indicated in patients after a fruitless first exploration.

Tumors of the body and tail are usually treated by distal pancreatectomy, those of the head by enucleation. There is a risk of pancreatic fistula, and duct damage can be unmasked by secretin injection. Occult tumors and hyperplasia may require “blind” progressive distal resection with blood sugar monitoring until the hypoglycemia is controlled, but this is something of a desperation measure. In malignant tumors, hypoglycemia may be controlled by diazoxide or somatostatin. Streptozotocin may control the syndrome and lead to prolongation of life. Like other malignant apudomas, these tumors are usually slow growing and relatively benign.

Hypoglycemia is of interest to the surgeon when it is due to an insulin-secreting tumor that may be amenable to cure by surgical excision. These tumors are rare, with a prevalence of about 0.5 per million adults per annum [1].

Reactive hypoglycemia may occur after gastrectomy when rapid gastric emptying leads to rapid absorption of glucose, causing an excessive insulin response and leading to hypoglycemia some 1½–2 hours after the meal; this is sometimes described as “late dumping.” Alcohol in a fasting individual is also a potent cause of hypoglycemia. Even commoner is excessive dosage of insulin or sulfonylurea drugs in the treatment of diabetes, particularly when this is not well controlled.

In this paper, attention will be concentrated upon patients with spontaneous organic hypoglycemia who fulfill Whipple’s triad [2]: (a) symptoms of hypoglycemia when fasting or after exertion, (b) associated with blood glucose levels below 2.4 mmol/L (45 mg/100 ml) and (c) relieved by glucose administered orally or intravenously. Organic hypoglycemia produces symptoms mainly as a result of neuroglycopenia and catecholamine output: nervousness, anxiety, behavioral abnormalities, epileptiform attacks, drowsiness, or even coma. The clinical picture may be bizarre and many patients have been found in mental hospitals. Diagnosis is often delayed for a year or more and long-standing hypoglycemia may lead to brain damage [3].

Investigation of Organic Hypoglycemia

In the presence of Whipple’s triad, insulinoma must be suspected and a program of investigation is required. The crucial test is the synchronous measurement of blood sugar and insulin. In normal individuals, insulin rises and falls more or less in parallel with the blood sugar level. With insulinoma, however, insulin levels are inappropriately high, even when the blood sugar is very low. The normal feedback mechanism, in which hypoglyce-
emia is associated with inhibition of insulin release, is lost. The ratio of insulin (μU/ml) to blood glucose (mg/100 ml) is normally less than 0.4, but most insulinoma patients have a ratio greater than 1.0 [4].

Repeated observations are required and it is usually necessary to fast the patient overnight, which will produce hypoglycemia in 4 out of 5 patients [5]. Fasting for 48 hours followed by brisk exercise will produce hypoglycemia in 98% of insulinomas [6]. Others have used prolonged fasting up to 72 hours with equal success [1, 7].

Many tests have been devised and become popular as a means of avoiding prolonged fasting and thus saving expensive hospital time. One is the tolbutamide test. This sulfonylurea drug stimulates the release of insulin from the beta cells and has been widely used as a “short” screening test [8]. It may, however, cause dangerous levels of hypoglycemia in patients with insulinoma and is, therefore, not now widely recommended [5].

In the presence of an islet-cell tumor, l-leucine causes a sharp rise of insulin and fall of blood sugar, but it has little effect in normal individuals. False-negatives and false-positives are both common, so the test is no longer in general use.

Glucagon, given in a dose of 1 mg intravenously, stimulates the release of insulin, but in normal subjects the effect is more than counterbalanced by mobilization of glucose from liver glycogen. With an islet-cell tumor, a rise to 150 μU/ml is considered diagnostic, whereas in normal individuals the insulin level should not exceed 100 μU/ml. There are false-negative results in about 1/4 of all insulinomas [7]; thus, the test is of only limited value.

As with gastrin in the Zollinger-Ellison syndrome, infusion of calcium has been shown to cause release of insulin from insulinomata, and consequent hypoglycemia [9]. There are reports of false-negatives [10], and in one series 6 out of 6 insulinoma patients failed to respond [11]. The test may be dangerous in patients with heart disease or arrhythmia and must, therefore, be used with great caution or abandoned.

As levels of glycosylated hemoglobin (Hb A1) are elevated in poorly controlled diabetics and reflect the performance of blood sugar over a period of weeks, it could be anticipated that levels would be lowered in patients with insulinoma, giving a better guide to the hypoglycemic state than the clinician can obtain from isolated blood sugar examinations. Positive results have been reported in 1 patient [12], but other investigators have not confirmed its value [13]. In our experience in 3 insulinoma patients, HbA1 was normal in all 3.

If commercial insulin is given intravenously, normal islets will be suppressed but an insulinoma will continue to secrete and assay of proinsulin and C-peptide may be useful. Proinsulin, the “big insulin” precursor, can be measured by radioimmunoassay. In the normal individual very little is secreted; but with insulinoma, and particularly malignant insulinoma, proinsulin may amount to as much as 50% of the total. This test may be of particular value in the preoperative diagnosis of malignancy and in the postoperative monitoring of these patients. Within the beta-cell, proinsulin is split, releasing insulin and C-peptide on an equimolar basis. C-peptide levels thus indicate beta-cell activity. C-peptide can be estimated after injection of exogenous insulin, when its concentration should be very low. With insulinoma, however, C-peptide will not be suppressed and will roughly parallel insulin levels [14].

Insulin derived from fish is biologically active in humans but is not picked up by an orthodox immunoassay of human insulin. It is, therefore, possible to cause hypoglycemia with complete suppression of endogenous insulin, but without suppression of the insulin produced by an islet-cell tumor [15].

Of all these tests, prolonged fasting is the simplest, safest, and most generally useful. Stimulation with tolbutamide or calcium infusion is potentially dangerous. The leucine and glucagon tests are not sufficiently specific to be of much practical value. The suppression tests are of particular value in the detection of self-induced hypoglycemia.

Factitious Hypoglycemia

In recent years increasing numbers of patients with self-induced hypoglycemia have been reported, particularly in the United States. These patients are usually doctors, nurses, paramedical personnel, diabetics or their relatives, who inject themselves with insulin for obscure reasons and present with often bizarre symptoms [16, 17]. If this possibility exists, antibodies to commercial insulin should be sought and their presence would tend to confirm the suspicion. More precise evidence can be derived from C-peptide and proinsulin estimations: both will be raised in insulinoma but not in self-induced hypoglycemia. The difficulty, however, does not end here, since sulfonylureas, e.g., tolbutamide, may be taken to produce factitious hypoglycemia. It is possible to estimate blood levels of tolbutamide and related drugs and thus unmask the factitious patient [18]. Rarely, an insulinoma may develop in a diabetic patient [19] and this may cause considerable confusion.

Organic Hypoglycemia due to Non–islet cell Tumors

Even when true organic hypoglycemia, without self-administration, has been proven, it is still not