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Reactive hypoglycaemia

Insulin, the sulphonylureas, and alcohol cause most of the hypoglycaemic episodes that bring people to hospital.[1,2] Nevertheless, many conditions may occasionally cause hypoglycaemia,[3-5] itself a great mimic, "capable of almost limitless combinations of signs and symptoms."[6]

Hypoglycaemia is conveniently separated into the reactive (postprandial) type, with predominantly adrenergic symptoms two to five hours after meals, and the more ominous fasting hypoglycaemia often with symptoms of neuroglycopenia. Here I am principally concerned with reactive hypoglycaemia. This may occur after intestinal surgery, as part of an endocrine disorder (early diabetes mellitus, cortisol deficiency, hypothyroidism), or as a functional disturbance.[5] In patients with suspected hypoglycaemia the first two causes of reactive hypoglycaemia are usually easily excluded, and the distinction has to be made between insulinoma, functional hypoglycaemia (both rare), and symptoms not due to hypoglycaemia at all.

Britain has been largely spared the epidemic of hypoglycaemia currently afflicting the United States.[7] Some patients and doctors there have wrongly attributed a wide variety of symptoms to hypoglycaemia, failing to recognise the importance of Whipple's triad (hypoglycaemic symptoms, low plasma glucose, and response to glucose ingestion) for the diagnosis.[5] In some cases the result of the prolonged oral glucose tolerance test has been wrongly interpreted; certainly it is unwise to diagnose reactive hypoglycaemia on grounds of chemical hypoglycaemia alone. One study has shown that among 650 normal subjects given glucose 100 g orally plasma glucose trough values of $<2{\cdot}6$ mmol/l were found in 10% and of $<2{\cdot}16$ mmol/l in 2·5% of subjects.[8] Furthermore, in 118 patients with suspected hypoglycaemia chemical hypoglycaemia coincided with symptoms in only 16. The symptoms in the remaining 102 patients did not correlate with meals, the results of oral glucose tolerance tests, or the blood glucose concentration. Fourteen of these patients with "non-hypoglycaemia," however, experienced symptoms they thought were due to hypoglycaemia after a placebo oral glucose tolerance test.[8]

Charles *et al* have argued that if reactive hypoglycaemia relates causally to symptoms in daily life then hypoglycaemia should be demonstrable after mixed meals. They did not find this in 18 patients who had developed reactive hypoglycaemia after an oral glucose tolerance test, although 14 of them had symptoms. These authors coined the term idiopathic postprandial syndrome to distinguish patients with postprandial symptoms but without hypoglycaemia.[9] Similar findings have been reported by others using mixed meals in patients with suspected reactive hypoglycaemia. By contrast patients with insulinoma are symptomatically hypoglycaemic after both mixed meals and oral glucose tolerance tests.[10]

It has been suggested that functional reactive hypoglycaemia is a useful diagnostic label because "many patients cherish this diagnosis even when it is not supported by chemical tests since it is not life threatening, merits professional concern, can be treated by dietary manipulation and thus serves both patient and practitioner."[11] These and other authors have, however, emphasised that misdiagnosing functional hypoglycaemia may delay detection and treatment of psychiatric illness.[11-13]

The Minnesota multiphasic personality inventory was applied to 35 men and 63 women attending the Mayo Clinic for evaluation of possible reactive hypoglycaemia.[12] The scores for women on the hypochondriasis, depression, and hysteria scales conformed to a conversion pattern typical of those "who displace emotional problems to the soma and are resistant to psychological intervention or interpretations of symptoms." (Men also showed a trend towards this pattern.) The authors concluded that emotional disturbance is common in these patients but found no evidence that it was due to hypoglycaemia.[12] Others have reported similar findings from the Minnesota multiphasic personality inventory.[13]

A recent study entailing clinical psychiatric assessments of patients with suspected reactive hypoglycaemia showed that only four out of 130 had true functional hypoglycaemia; 58 had "somatoform" disorders ("conversion symptoms without significant depression were imposed on a background of dependent, histrionic, or schizoid personality disorder"), 46 had mainly depressive affective disorders, and only 26 were without evidence of psychiatric disorder.[11] Symptoms complained of by the subgroup with "somatoform" disorders included panic, depression, crying spells, good and bad days, lightheadedness, dizziness, hyperventilation, fatigue, agitation, tremulousness, palpitation, irritability, weight loss or gain, drowsiness, insomnia, loss of memory, decreased libido, frigidity, headaches, dimness of vision, claustrophobia, and globus.[11]

How, then, should patients with a self diagnosis of hypoglycaemia or postprandial symptoms suggestive of reactive hypoglycaemia be managed? A careful clinical history (including psychiatric assessment) and examination are required because of the non-specific symptoms, together with confirmation of the diagnosis by showing the presence of Whipple's triad. The unphysiological prolonged oral glucose tolerance test should be abandoned in assessing these patients; a better approach is to document hypoglycaemia after ordinary meals. Because reliable techniques for collecting blood samples at home and subsequent laboratory analysis are available the initial assessment of glucose concentrations can be made on an outpatient basis. If chemical hypoglycaemia is associated with the relevant symptoms then further investigation is recommended. A 72 hour fast (in hospital) provokes hypoglycaemia in nearly all patients with insulinoma, and the diagnosis is confirmed by finding inappropriately raised plasma insulin concentrations.[14]

Reactive hypoglycaemia is rare if the correct diagnostic criteria are applied; if those patients with impaired glucose tolerance, previous intestinal surgery, or endocrine disorders are identified then functional hypoglycaemia, so often misdiagnosed, is rare indeed. A diet low in refined sugar and

high in fibre, without excess caffeine containing drinks or alcohol, should keep the patient with true functional hypoglycaemia free of symptoms.

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Abuse of fresh frozen plasma

Replacing the blood volume of a patient over 24 hours or less may lead to widespread bleeding because of defective coagulation. Stored blood contains virtually no functioning platelets, and factor V and factor VIII deteriorate during storage.[1] A massive transfusion is therefore accompanied by dilution of these clotting factors, but bleeding after massive transfusion is more likely to be caused by consumption of clotting factors.[2] Disseminated intravascular coagulopathy commonly follows trauma, sepsis, and hypotension—conditions that often necessitate a large transfusion. Because disordered blood coagulation may follow the transfusion of large volumes of stored blood it is often suggested that one or two units of fresh frozen plasma should be transfused routinely with every four units of stored blood.[3] Yet nothing but anecdote supports this contention.

Many patients who receive a massive transfusion do not bleed abnormally, and one study showed that transfusing one unit of fresh frozen plasma for every three of whole blood or packed red cells did not reduce the amount of blood transfused.[4] If abnormal bleeding does occur, thrombocytopenia, not deficiency of factor V or VIII, is the likeliest cause.[5] A consensus development conference of the National Institutes of Health therefore recommended in 1985 that fresh frozen plasma should not be given as a supplement to blood transfusion unless an abnormality of blood coagulation was suspected on clinical grounds and had been confirmed in the laboratory.[6]

Fresh frozen plasma is often given as a volume expander, and an American study found that volume replacement was the sole indication for using half of the fresh frozen plasma supplied by one transfusion centre.[7] The consensus conference advised that fresh frozen plasma should not be used for this purpose because safer, cheaper, and more readily available volume expanders exist.

Furthermore, the indiscriminate use of fresh frozen plasma is hazardous. Blood, or any of its unpasteurised derivatives, may transmit infection, including hepatitis and the acquired immune deficiency syndrome. Occasionally, the antibodies present in plasma may produce harmful effects—for example, leucoagglutinins may cause pulmonary infiltrates.[8] Anti-A and anti-B in plasma may destroy the recipient's red cells, although this hazard can be avoided by using fresh frozen plasma that is ABO compatible. Fresh frozen plasma may also cause hypersensitivity reactions.[8] To take a wider view, any fresh plasma retained at a regional transfusion centre and supplied as fresh plasma to hospitals is withheld from the national Blood Products Laboratory. In north west London so much fresh frozen plasma is now called for by doctors that the transfusion centre cannot send its quota to the Blood Products Laboratory, which needs it to manufacture factor VIII and, coincidentally, albumin. Consuming fresh frozen plasma as an unnecessary adjunct to transfusion thus delays Britain's self sufficiency in factor VIII.

The proper indications for using fresh frozen plasma are few. The commonest indication is abnormal bleeding in which a clotting defect has been proved. This category includes some patients with established disseminated intravascular coagulopathy and some with liver disease who are either actively bleeding or about to undergo major surgery.[9] Whether fresh frozen plasma or clotting factor concentrates should be given prophylactically to patients with liver disease before needle biopsy is debatable[10]; bleeding at biopsy seems to be unrelated to the prothrombin time.[11] Anticoagulant action by compounds of the coumarin type may be reversed within 6-12 hours with vitamin K, but in more urgent circumstances fresh frozen plasma is required. Fresh frozen plasma may also be indicated in thrombotic thrombocytopenic purpura, although "outdated" plasma has been reported to be equally effective in this uncommon condition.[12,13] Finally, fresh frozen plasma is required for patients with rare isolated factor deficiencies—of, for instance, factor V and factor X—for which specific concentrates are unavailable.

Surgeons and anaesthetists are the greediest consumers of fresh frozen plasma, and often they are misusing it. They should restrict their demand for this scarce resource.[14]

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