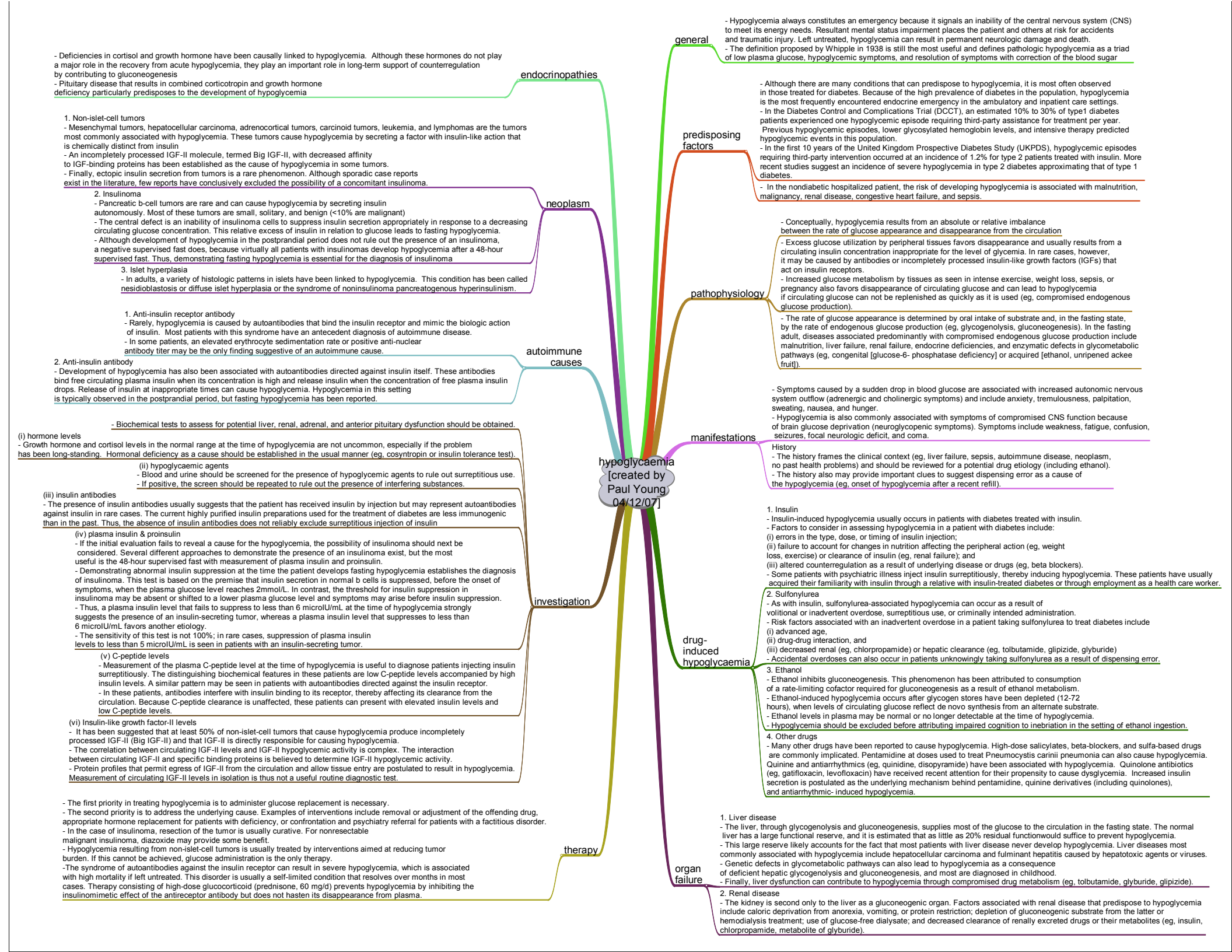
hypoglycaemia [created by Paul Young 04/12/07]
general
- Hypoglycemia always constitutes an emergency because it signals an inability of the central nervous system (CNS) to meet its energy needs. Resultant mental status impairment places the patient and others at risk for accidents and traumatic injury. Left untreated, hypoglycemia can result in permanent neurologic damage and death.
- The definition proposed by Whipple in 1938 is still the most useful and defines pathologic hypoglycemia as a triad of low plasma glucose, hypoglycemic symptoms, and resolution of symptoms with correction of the blood sugar
predisposing factors
- Although there are many conditions that can predispose to hypoglycemia, it is most often observed in those treated for diabetes. Because of the high prevalence of diabetes in the population, hypoglycemia is the most frequently encountered endocrine emergency in the ambulatory and inpatient care settings.
- In the Diabetes Control and Complications Trial (DCCT), an estimated 10% to 30% of type1 diabetes patients experienced one hypoglycemic episode requiring third-party assistance for treatment per year. Previous hypoglycemic episodes, lower glycosylated hemoglobin levels, and intensive therapy predicted hypoglycemic events in this population.
- In the first 10 years of the United Kingdom Prospective Diabetes Study (UKPDS), hypoglycemic episodes requiring third-party intervention occurred at an incidence of 1.2% for type 2 patients treated with insulin. More recent studies suggest an incidence of severe hypoglycemia in type 2 diabetes approximating that of type 1 diabetes.
- In the nondiabetic hospitalized patient, the risk of developing hypoglycemia is associated with malnutrition, malignancy, renal disease, congestive heart failure, and sepsis.
pathophysiology
- Conceptually, hypoglycemia results from an absolute or relative imbalance between the rate of glucose appearance and disappearance from the circulation
- Excess glucose utilization by peripheral tissues favors disappearance and usually results from a circulating insulin concentration inappropriate for the level of glycemia. In rare cases, however, it may be caused by antibodies or incompletely processed insulin-like growth factors (IGFs) that act on insulin receptors.
- Increased glucose metabolism by tissues as seen in intense exercise, weight loss, sepsis, or pregnancy also favors disappearance of circulating glucose and can lead to hypoglycemia if circulating glucose can not be replenished as quickly as it is used (eg, compromised endogenous glucose production).
- The rate of glucose appearance is determined by oral intake of substrate and, in the fasting state, by the rate of endogenous glucose production (eg, glycogenolysis, gluconeogenesis). In the fasting adult, diseases associated predominantly with compromised endogenous glucose production include malnutrition, liver failure, renal failure, endocrine deficiencies, and enzymatic defects in glycometabolic pathways (eg, congenital [glucose-6- phosphatase deficiency] or acquired [ethanol, unripened ackee fruit]).
manifestations
- Symptoms caused by a sudden drop in blood glucose are associated with increased autonomic nervous system outflow (adrenergic and cholinergic symptoms) and include anxiety, tremulousness, palpitation, sweating, nausea, and hunger.
- Hypoglycemia is also commonly associated with symptoms of compromised CNS function because of brain glucose deprivation (neuroglycopenic symptoms). Symptoms include weakness, fatigue, confusion, seizures, focal neurologic deficit, and coma.
History
- The history frames the clinical context (eg, liver failure, sepsis, autoimmune disease, neoplasm, no past health problems) and should be reviewed for a potential drug etiology (including ethanol).
- The history also may provide important clues to suggest dispensing error as a cause of the hypoglycemia (eg, onset of hypoglycemia after a recent refill).
drug-induced hypoglycaemia
1. Insulin
- Insulin-induced hypoglycemia usually occurs in patients with diabetes treated with insulin.
- Factors to consider in assessing hypoglycemia in a patient with diabetes include:
(i) errors in the type, dose, or timing of insulin injection;
(ii) failure to account for changes in nutrition affecting the peripheral action (eg, weight loss, exercise) or clearance of insulin (eg, renal failure); and
(iii) altered counterregulation as a result of underlying disease or drugs (eg, beta blockers).
- Some patients with psychiatric illness inject insulin surreptitiously, thereby inducing hypoglycemia. These patients have usually acquired their familiarity with insulin through a relative with insulin-treated diabetes or through employment as a health care worker.
2. Sulfonylurea
- As with insulin, sulfonylurea-associated hypoglycemia can occur as a result of volitional or inadvertent overdose, surreptitious use, or criminally intended administration.
- Risk factors associated with an inadvertent overdose in a patient taking sulfonylurea to treat diabetes include
(i) advanced age,
(ii) drug-drug interaction, and
(iii) decreased renal (eg, chlorpropamide) or hepatic clearance (eg, tolbutamide, glipizide, glyburide)
- Accidental overdoses can also occur in patients unknowingly taking sulfonylurea as a result of dispensing error.
3. Ethanol
- Ethanol inhibits gluconeogenesis. This phenomenon has been attributed to consumption of a rate-limiting cofactor required for gluconeogenesis as a result of ethanol metabolism.
- Ethanol-induced hypoglycemia occurs after glycogen stores have been depleted (12-72 hours), when levels of circulating glucose reflect de novo synthesis from an alternate substrate.
- Ethanol levels in plasma may be normal or no longer detectable at the time of hypoglycemia.
- Hypoglycemia should be excluded before attributing impaired cognition to inebriation in the setting of ethanol ingestion.
4. Other drugs
- Many other drugs have been reported to cause hypoglycemia. High-dose salicylates, beta-blockers, and sulfa-based drugs are commonly implicated. Pentamidine at doses used to treat Pneumocystis carinii pneumonia can also cause hypoglycemia. Quinine and antiarrhythmics (eg, quinidine, disopyramide) have been associated with hypoglycemia. Quinolone antibiotics (eg, gatifloxacin, levofloxacin) have received recent attention for their propensity to cause dysglycemia. Increased insulin secretion is postulated as the underlying mechanism behind pentamidine, quinine derivatives (including quinolones), and antiarrhythmic- induced hypoglycemia.
organ failure
1. Liver disease
- The liver, through glycogenolysis and gluconeogenesis, supplies most of the glucose to the circulation in the fasting state. The normal liver has a large functional reserve, and it is estimated that as little as 20% residual functionwould suffice to prevent hypoglycemia.
- This large reserve likely accounts for the fact that most patients with liver disease never develop hypoglycemia. Liver diseases most commonly associated with hypoglycemia include hepatocellular carcinoma and fulminant hepatitis caused by hepatotoxic agents or viruses.
- Genetic defects in glycometabolic pathways can also lead to hypoglycemia as a consequence of deficient hepatic glycogenolysis and gluconeogenesis, and most are diagnosed in childhood.
- Finally, liver dysfunction can contribute to hypoglycemia through compromised drug metabolism (eg, tolbutamide, glyburide, glipizide).
2. Renal disease
- The kidney is second only to the liver as a gluconeogenic organ. Factors associated with renal disease that predispose to hypoglycemia include caloric deprivation from anorexia, vomiting, or protein restriction; depletion of gluconeogenic substrate from the latter or hemodialysis treatment; use of glucose-free dialysate; and decreased clearance of renally excreted drugs or their metabolites (eg, insulin, chlorpropamide, metabolite of glyburide).
therapy
- The first priority in treating hypoglycemia is to administer glucose replacement is necessary.
- The second priority is to address the underlying cause. Examples of interventions include removal or adjustment of the offending drug, appropriate hormone replacement for patients with deficiency, or confrontation and psychiatry referral for patients with a factitious disorder.
- In the case of insulinoma, resection of the tumor is usually curative. For nonresectable malignant insulinoma, diazoxide may provide some benefit.
- Hypoglycemia resulting from non-islet-cell tumors is usually treated by interventions aimed at reducing tumor burden. If this cannot be achieved, glucose administration is the only therapy.
-The syndrome of autoantibodies against the insulin receptor can result in severe hypoglycemia, which is associated with high mortality if left untreated. This disorder is usually a self-limited condition that resolves over months in most cases. Therapy consisting of high-dose glucocorticoid (prednisone, 60 mg/d) prevents hypoglycemia by inhibiting the insulinomimetic effect of the antireceptor antibody but does not hasten its disappearance from plasma.
investigation
- Biochemical tests to assess for potential liver, renal, adrenal, and anterior pituitary dysfunction should be obtained.
(i) hormone levels
- Growth hormone and cortisol levels in the normal range at the time of hypoglycemia are not uncommon, especially if the problem has been long-standing. Hormonal deficiency as a cause should be established in the usual manner (eg, cosyntropin or insulin tolerance test).
(ii) hypoglycaemic agents
- Blood and urine should be screened for the presence of hypoglycemic agents to rule out surreptitious use.
- If positive, the screen should be repeated to rule out the presence of interfering substances.
(iii) insulin antibodies
- The presence of insulin antibodies usually suggests that the patient has received insulin by injection but may represent autoantibodies against insulin in rare cases. The current highly purified insulin preparations used for the treatment of diabetes are less immunogenic than in the past. Thus, the absence of insulin antibodies does not reliably exclude surreptitious injection of insulin
(iv) plasma insulin & proinsulin
- If the initial evaluation fails to reveal a cause for the hypoglycemia, the possibility of insulinoma should next be considered. Several different approaches to demonstrate the presence of an insulinoma exist, but the most useful is the 48-hour supervised fast with measurement of plasma insulin and proinsulin.
- Demonstrating abnormal insulin suppression at the time the patient develops fasting hypoglycemia establishes the diagnosis of insulinoma. This test is based on the premise that insulin secretion in normal b cells is suppressed, before the onset of symptoms, when the plasma glucose level reaches 2mmol/L. In contrast, the threshold for insulin suppression in insulinoma may be absent or shifted to a lower plasma glucose level and symptoms may arise before insulin suppression.
- Thus, a plasma insulin level that fails to suppress to less than 6 microIU/mL at the time of hypoglycemia strongly suggests the presence of an insulin-secreting tumor, whereas a plasma insulin level that suppresses to less than 6 microIU/mL favors another etiology.
- The sensitivity of this test is not 100%; in rare cases, suppression of plasma insulin levels to less than 5 microIU/mL is seen in patients with an insulin-secreting tumor.
(v) C-peptide levels
- Measurement of the plasma C-peptide level at the time of hypoglycemia is useful to diagnose patients injecting insulin surreptitiously. The distinguishing biochemical features in these patients are low C-peptide levels accompanied by high insulin levels. A similar pattern may be seen in patients with autoantibodies directed against the insulin receptor.
- In these patients, antibodies interfere with insulin binding to its receptor, thereby affecting its clearance from the circulation. Because C-peptide clearance is unaffected, these patients can present with elevated insulin levels and low C-peptide levels.
(vi) Insulin-like growth factor-II levels
- It has been suggested that at least 50% of non-islet-cell tumors that cause hypoglycemia produce incompletely processed IGF-II (Big IGF-II) and that IGF-II is directly responsible for causing hypoglycemia.
- The correlation between circulating IGF-II levels and IGF-II hypoglycemic activity is complex. The interaction between circulating IGF-II and specific binding proteins is believed to determine IGF-II hypoglycemic activity.
- Protein profiles that permit egress of IGF-II from the circulation and allow tissue entry are postulated to result in hypoglycemia. Measurement of circulating IGF-II levels in isolation is thus not a useful routine diagnostic test.
autoimmune causes
1. Anti-insulin receptor antibody
- Rarely, hypoglycemia is caused by autoantibodies that bind the insulin receptor and mimic the biologic action of insulin. Most patients with this syndrome have an antecedent diagnosis of autoimmune disease.
- In some patients, an elevated erythrocyte sedimentation rate or positive anti-nuclear antibody titer may be the only finding suggestive of an autoimmune cause.
2. Anti-insulin antibody
- Development of hypoglycemia has also been associated with autoantibodies directed against insulin itself. These antibodies bind free circulating plasma insulin when its concentration is high and release insulin when the concentration of free plasma insulin drops. Release of insulin at inappropriate times can cause hypoglycemia. Hypoglycemia in this setting is typically observed in the postprandial period, but fasting hypoglycemia has been reported.
neoplasm
1. Non-islet-cell tumors
- Mesenchymal tumors, hepatocellular carcinoma, adrenocortical tumors, carcinoid tumors, leukemia, and lymphomas are the tumors most commonly associated with hypoglycemia. These tumors cause hypoglycemia by secreting a factor with insulin-like action that is chemically distinct from insulin
- An incompletely processed IGF-II molecule, termed Big IGF-II, with decreased affinity to IGF-binding proteins has been established as the cause of hypoglycemia in some tumors.
- Finally, ectopic insulin secretion from tumors is a rare phenomenon. Although sporadic case reports exist in the literature, few reports have conclusively excluded the possibility of a concomitant insulinoma.
2. Insulinoma
- Pancreatic b-cell tumors are rare and can cause hypoglycemia by secreting insulin autonomously. Most of these tumors are small, solitary, and benign (<10% are malignant)
- The central defect is an inability of insulinoma cells to suppress insulin secretion appropriately in response to a decreasing circulating glucose concentration. This relative excess of insulin in relation to glucose leads to fasting hypoglycemia.
- Although development of hypoglycemia in the postprandial period does not rule out the presence of an insulinoma, a negative supervised fast does, because virtually all patients with insulinomas develop hypoglycemia after a 48-hour supervised fast. Thus, demonstrating fasting hypoglycemia is essential for the diagnosis of insulinoma
3. Islet hyperplasia
- In adults, a variety of histologic patterns in islets have been linked to hypoglycemia. This condition has been called nesidioblastosis or diffuse islet hyperplasia or the syndrome of noninsulinoma pancreatogenous hyperinsulinism.
endocrinopathies
- Deficiencies in cortisol and growth hormone have been causally linked to hypoglycemia. Although these hormones do not play a major role in the recovery from acute hypoglycemia, they play an important role in long-term support of counterregulation by contributing to gluconeogenesis
- Pituitary disease that results in combined corticotropin and growth hormone deficiency particularly predisposes to the development of hypoglycemia