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Spontaneous hypoglycemia: A narrative review

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Abstract

Hypoglycemia is a common medical problem and is mostly iatrogenic in patients with diabetes mellitus. In contrast, spontaneous hypoglycemia is relatively uncommon and poses a significant diagnostic challenge. A definitive diagnosis can be made for spontaneous hypoglycemia by using a systematic approach. After confirming the presence of a hypoglycemic disorder, a detailed history should be taken which often suggests a specific underlying cause and can guide further testing. A complete hypoglycemic blood panel must be analyzed (Plasma glucose, insulin, C-peptide, proinsulin, Beta-hydroxybutyrate, sulphonylurea screen, insulin autoantibody) during a spontaneous event or after provoked by a fasting test/mixed meal challenge test, and patients must be categorized based on their clinical status (seemingly well and unwell). *[J Assoc Clin Endocrinol Diabetol Bangladesh,* July 2024;3(2)*: 58-64]*

Keywords: Hypoglycemia, spontaneous, diagnostic challenge

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Introduction

Clinical hypoglycemia is the term used to describe a situation in which serum or plasma glucose levels drop to the point when symptoms and/or signs, such as impaired brain function, occur. The clinical manifestations of hypoglycemia are nonspecific. Besides, it is not uncommon to find very low blood glucose concentrations in asymptomatic people, especially young women and children. A measured low blood glucose can be artifactual. For these reasons, it is not possible to pinpoint a single plasma glucose concentration that can categorically define hypoglycemia, Therefore, hypoglycemia is confirmed by documentation of Whipple's triad: symptoms, signs, or both that are indicative of hypoglycemia, and a low plasma glucose, and how those symptoms or signs go away when plasma glucose levels are raised.[1] If Whipple's triad is not fulfilled, the patient could be subjected to needless testing, expenses, and other risks without any prospect of benefit.

Glucose homeostasis and counter-regulation

Under normal physiological conditions, our brain depends on the continuous supply of glucose for normal functioning.[2] This is due to the brain's inability to produce glucose, effectively utilize other alternative fuels efficiently, or store glucose for longer than a few minutes supply in the form of glycogen. Because arterial plasma glucose concentration directly influences blood-to-brain glucose transport, this necessitates maintaining plasma glucose levels within the normal range. Normally, counterregulatory systems efficiently prevent hypoglycemia. Crucial physiological defenses include 1) a reduction in insulin release when glucose levels drop within the physiological range, 2) an increase in glucagon secretion, and 3) an increase in epinephrine secretion, the last two occurring when glucose levels drop slightly below the physiological range.[3]

Defense against persistent hypoglycemia involves the release of growth hormone (GH) and cortisol. Plasma glucose levels will continue to decline if these defenses are unable to stop the episode. The symptoms that cause the behavioral defense of food consumption usually start to show up at a plasma glucose level of about 55 mg/dl (3.0 mmol/liter). When plasma glucose reaches around 3

mmol/L, there is almost no insulin secretion, C-peptide levels are below 0.6 ng/ml (0.2 nmol/liter), proinsulin levels are below 5.0 pmol/liter, and plasma insulin levels are below 3 U/ml (18 pmol/liter).[4,5] Due to the ability to greatly increase endogenous glucose production, hypoglycemia typically comes from very low rates of glucose synthesis or low rates of glucose production relative to high rates of glucose use.[6]

Symptoms of hypoglycemia in a non-diabetic person

Hypoglycemia symptoms are classified as either neurogenic or autonomic (due to sympathetic stimulation induced by hypoglycemia) and neuroglycopenic (resulting from brain glucose deprivation).[7] Awareness of hypoglycemia arises from the perception of neurogenic symptoms, which are predominantly sympathetic neural rather than adrenomedullary. Though most neurogenic symptoms, such as tremors, anxiety, and palpitation, are adrenergic, some symptoms, such as sweating and hunger, are cholinergic.[8] The symptoms of neuroglycopenia include loss of consciousness, exhaustion, disorientation, seizures, and cognitive impairment. Neurological recovery occurs completely when the glucose level is raised; nevertheless, this is not always the case. If hypoglycemia is prolonged and profound, it can lead to brain death.[2] Signs of hypoglycemia like sweating, pallor, tachycardia, and behavioral changes are often subtle. A diagnostic assessment for spontaneous hypoglycemia is necessary even in the event of a single neuroglycopenia episode.

Classification of spontaneous hypoglycemia

The traditional classification of hypoglycemia in persons without diabetes, postabsorptive (fasting) and postprandial (reactive) hypoglycemia, has been challenged.[6] Individuals with insulinomas, who often experience hypoglycemia mostly while fasting, may experience postprandial hypoglycemia. Post-gastric bypass patients, who usually have postprandial hypoglycemia, may also suffer symptoms in a fasting state. Some conditions, like factitious hypoglycemia, are hard to classify into fasting or postprandial. Previously known as 'reactive hypoglycemia', postprandial symptoms lacking Whipple's triad signify a functional disease for which an oral glucose tolerance test is not recommended, and symptoms are not caused by hypoglycemia.[9] It is more useful to determine whether the patient appears to be in good health or if they are dealing with a potentially relevant illness or therapy. This will help the clinician to categorize the patient more effectively. Regarding the latter, medication must be taken into consideration for any patient presenting with hypoglycemia.

Causes of spontaneous hypoglycemia

The causes of hypoglycemia are outlined in Table I. Drugs are the most common cause of hypoglycemia.[10] Apart from insulin and insulin secretagogues, additional drugs that are considered offending include alcohol, antimalarials, quinolones, ACE inhibitors, indomethacin, lithium, and several more.[10] Hypoglycemia frequently occurs in sepsis and other serious conditions like renal or liver failure and rarely in adrenal insufficiency.10 Hypoglycemia caused by endogenous hyperinsulinism is rare.[10] It can be accidental, surreptitious, or even malicious, which is very challenging to diagnose.[11] Those who have Roux-en-Y gastric bypass for obesity frequently experience hypoglycemia. Hypoglycemia can be caused by an antibody to insulin or insulin receptor, which is associated with a very high level of insulin.[12] The nonislet tumor that causes hypoglycemia is often clinically obvious.

Table I: Causes of spontaneous hypoglycemia in adults[10]

Unwell individual
√ Drugs, alcohol
√ Sepsis, malaria
√ Liver failure
√ Renal failure
√ Adrenal insufficiency
√ Malignancy (nonislet tumor)
Seemingly well individual
√ Insulinoma
√ Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)
√ Post gastric bypass hypoglycemia
√ Autoimmune hypoglycemia
√ Accidental, surreptitious, or malicious hypoglycemia

Evaluation of spontaneous hypoglycemia

In healthy persons, a mean plasma glucose concentration of about 55 mg/dl (3.0 mmol/liter) is the threshold at which hypoglycemia symptoms appear.[3] However, in individuals with recurrent hypoglycemia, the glycemic thresholds for hypoglycemic symptoms shift to lower plasma glucose concentrations. Lower plasma glucose concentrations occur after prolonged fasting in healthy

Table-II: Interpretation of laboratory tests in spontaneous hypoglycemia[10]

Symptoms, signs, or both	Glucose (mg/dL)/ (mmol/L)	Insulin (microU/mL)/ (pmol/L)	C-peptide (nmol/L)/ (ng/mL)	Proinsulin (pmol/L)	Beta-hydroxybutyrate (mmol/L)	Glucose increase after glucagon (mg/dL)/(mmol/L)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
No	<55/3	<3/20.8	<0.2/0.6	<5	<25/1.4	No	No	Normal	
Yes	<55	>>3	<0.2	<5	>2.7	>25	No	Neg (Pos)	Exogenous insulin
					≤2.7				
Yes	<55	≥3	≥0.2	≥5		>25	No	Neg	Insulinoma, NIPHS, PGBH
					≤2.7				
Yes	<55	≥3	≥0.2	≥5		>25	Yes	Neg	Oral hypoglycemic agent
					≤2.7				
Yes	<55	>>3	>>0.2χ	>>5χ		>25	No	Pos	Insulin autoimmune IGFμ
					≤2.7				
Yes	<55	<3	<0.2	<5		>25	No	Neg	Not insulin (or
Yes	<55	<3	<0.2	<5	≤2.7	<25	No	Neg	IGF)-mediated
					>2.7				

IGF: insulin-like growth factor; Neg: negative; NIPHS: noninsulinoma pancreatogenous hypoglycemia syndrome; PGBH: post-gastric bypass hypoglycemia; Pos: positive, Neg: negative
χFree C-peptide and proinsulin concentrations are low
μIncreased pro-IGF-2, free IGF-2, IGF-2/IGF-1 ratio
Adapted from: Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:709

individuals, particularly in women and children, with no accompanying symptoms or signs. This is because the brain can use alternate circulating fuels, specifically ketones.[3] It is impossible to pinpoint a single plasma glucose level that definitively characterizes hypoglycemia due to all of these factors.

The diagnosis of a true hypoglycemic disorder requires the fulfilment of specific criteria known as Whipple's triad.

Whipple's triad comprises the following:

- Symptoms consistent with hypoglycemia
- A low plasma glucose concentration is measured by a laboratory assay (not a glucose meter or continuous glucose monitor) when symptoms are present
- Resolution of symptoms after the plasma glucose level is raised

The evaluation is initially guided by the history (including any medication exposure), the physical examination, and an extensive review of the available laboratory results (Figure 1). These typically offer hints about the underlying cause of hypoglycemia or rule out hypoglycemia brought on by known drugs, serious diseases, hormone deficits, or nonislet cell tumors (Table 1). Even though adrenocortical insufficiency is not usually found to be the cause of hypoglycemia in adults without additional clinical symptoms, testing adrenocortical function is a reasonable course of action.

When a person appears healthy, the differential diagnosis can be limited to two main conditions: endogenous hyperinsulinism and accidental, surreptitious, or even malicious hypoglycemia.[6] A thorough evaluation of the former option ought to come before a methodical examination of the latter. Those who are aware of and have access to glucose-lowering drugs are more likely to experience surreptitious hypoglycemia.[11] An administration of insulin or an insulin secretagogue might cause malicious hypoglycemia.[11]

Episodes of neuroglycopenia caused by endogenous hyperinsulinemic hypoglycemia, which typically occur during fasting but can sometimes occur after a meal, are the clinical hallmarks of insulinoma.[9] It occurs around once per 250,000 patients per year.[13] It may happen at any age, with a slight female predilection. Less than 10% of individuals have multiple tumors, multiple endocrine neoplasia, type 1 (MEN-1) syndrome, or malignant insulinomas.[14]

The characteristic feature of noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is episodes of neuroglycopenia brought on by endogenous hyperinsulinemic hypoglycemia, which typically occurs after a meal but sometimes with fasting as well.[15] Men

are significantly more affected than women. The pancreatic abnormality is diffuse islet involvement with nesidioblastosis, which is characterized by islet hypertrophy and occasionally hyperplasia along with enlarged and hyperchromatic cell nuclei. Radiological localization procedures are typically negative. To diagnose islet hyperfunction, a positive selective arterial calcium stimulation test is necessary.[16] The findings of the calcium stimulation test should guide partial pancreatectomy, which usually improves the condition. NIPHS is far less common than insulinomas.

People of Japanese or Korean origin are more susceptible to a rare condition called autoimmune hypoglycemia, which is caused by the development of antibodies to natural insulin.[17] Those who have this condition frequently have a history of autoimmune diseases or have taken medications that include sulfhydryl. During the late postprandial phase, symptoms manifest as the insulin that was generated in response to the meal and then bound to the circulating antibody dissociates from the antibody inappropriately.[18] Extremely high insulin level during hypoglycemia is one indicator of the diagnosis. Hypoglycemia can range in severity from moderate, which can be managed with lifestyle modifications, to severe, for which there is no proven treatment other than intragastric glucose infusion. The finding of extremely high titer blood insulin antibodies typically leads to the diagnosis.

When a caregiver observes a seemingly well patient exhibiting symptoms, the most efficient diagnostic approach is to collect plasma for the assessment of glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate, and circulating oral hypoglycemic agents (ideally, all sulfonylureas and glinides that are currently available), and then use a 1.0 mg intravenous glucagon injection to treat the hypoglycemia while monitoring the plasma glucose response.[5,10] This data will assist in distinguishing between endogenous (and exogenous) hyperinsulinism and other hypoglycemic causes (Table II). Insulin antibodies, which do not need to be found at the moment of hypoglycemia, can identify autoimmune hypoglycemia.

The inability of insulin secretion to decrease to extremely low levels when plasma glucose concentrations drop to hypoglycemic levels- is the primary pathophysiological characteristic of endogenous hyperinsulinism. Hypoglycemia is caused by low rates of glucose synthesis rather than high rates of glucose utilization.[19] Therefore, it is not necessary for plasma insulin, C-peptide, and proinsulin concentrations to be high in comparison to normal euglycemic values; rather, they should only be abnormally high when fasting plasma glucose levels are low.[6] When the fasting plasma glucose concentrations are less than 55 mg/dl (3.0 mmol/liter), critical diagnostic findings include plasma insulin concentrations of at least 3 U/ml (18 pmol/liter), plasma C-peptide concentrations of at least 0.6 ng/ml (0.2 nmol/liter), the beta-hydroxybutyrate level is low (≤ 2.7 mmol/L) and plasma proinsulin concentrations of at least 5.0 pmol/l (table II).[6] These criteria presuppose the absence of other conditions, such as renal failure.

Even after a 72-hour fast, a patient with an insulinoma may occasionally not meet these criteria, and a few have plasma insulin levels below 3 U/ml (18 pmol/liter) during fasting hypoglycemia, but plasma C-peptide levels are usually 0.6 ng/ml (0.2 mmol/liter), or greater and plasma proinsulin levels are usually 5.0 pmol/liter or greater in the latter patients.[20] In one study, for instance, all 32 patients with an insulinoma met the proinsulin and C-peptide requirements, while only 29 of the patients met the plasma insulin criterion.[20] Biological evidence of insulin (or IGF) excess is provided by plasma beta-hydroxybutyrate levels of 2.7 mmol/liter or less and an increase in plasma glucose concentration of at least 25 mg/dl (1.4 mmol/liter) following intravenous glucagon (glucagon challenge test), the latter of which indicates preserved hepatic glycogen stores.[21] So, if endpoints are not met even after 72 hours fast, the Glucagon challenge test can provide additional clues for the diagnosis of endogenous insulin/IGF-mediated hypoglycemia.

In cases when a patient has a history of suggestive spells and Whipple's triad is unclear, it is desirable to simulate hypoglycemia-causing situations and obtain the required testing during a spontaneous hypoglycemic episode.[6] It is possible to create hypoglycemia in patients who have a history of it when fasting by avoiding food, and it is possible to create hypoglycemia in patients who have a history of it after eating by providing them with a meal that is likely to cause a hypoglycemic episode.[10] If these measures don't work, the patient with suspected fasting hypoglycemia should adhere to a longer, supervised fast. The objective is to hold off on breaking the fast until Whipple's triad is verified or the plasma glucose level falls to less than 55 mg/dl (3.0 mmol/liter). In less than 72 hours, the majority of insulinoma patients meet these diagnostic requirements.[22] In fact, in roughly two-thirds of affected patients, it happens in less than 24 hours, and in the great majority of cases, in less than 48 hours.[22] Doing a mixed-meal test is recommended when a

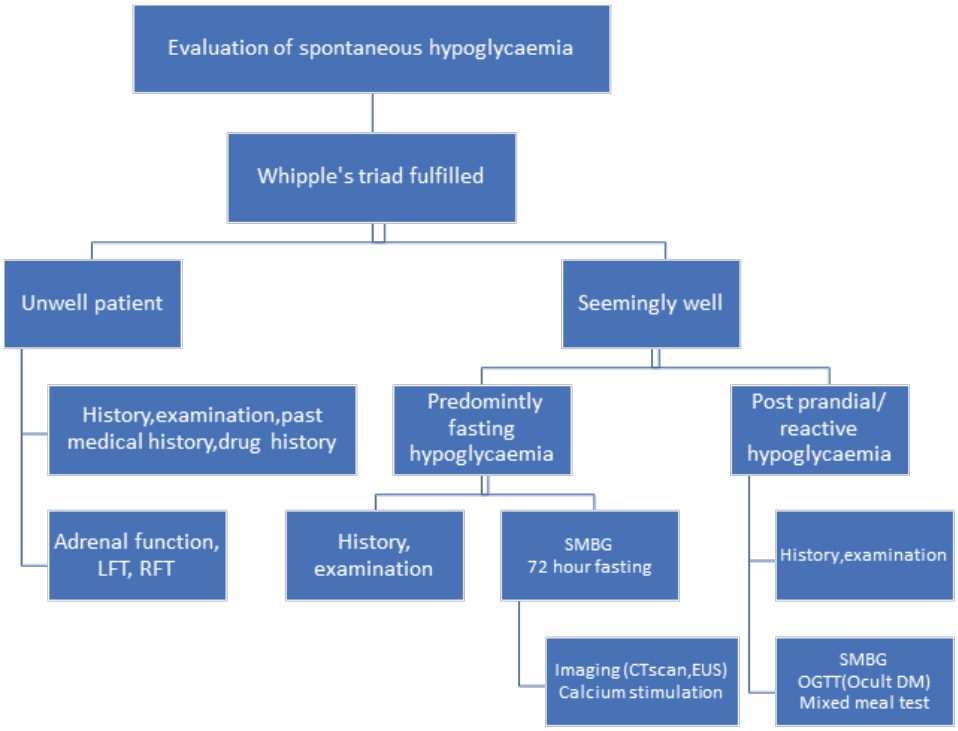

Figure-1: Flowchart for the evaluation of spontaneous hypoglycemia
SMBG- self-monitoring of blood glucose, EUS- endoscopic ultrasound, LFT- liver function tests, RFT- renal function tests

patient's history suggests postprandial hypoglycemia. Follow-up should be provided for five hours after the meal, which should comprise the items the patient has determined are most likely to cause hypoglycemia. When assessing possible postprandial hypoglycemia, an oral glucose tolerance test should not be performed.[23] However, it's still uncertain how to interpret the mixed-meal test. Currently, the criteria created above while going through fasting test, are applied to the findings of a mixed-meal challenge test (Table II).[5]

If a patient has a history of Whipple's triad, abnormally elevated levels of plasma insulin, C-peptide, and proinsulin, no measurable levels of oral hypoglycemic medications during fasting hypoglycemia, and no circulating insulin antibodies, the patient most likely has an insulinoma.[6] Nonetheless, accidental, surreptitious, or malicious hypoglycemias are challenging to diagnose. A high degree of clinical suspicion and an examination into potential offending agent sources, including a review of the patient's prescription regimen, provide the basis for these diagnoses. However, endogenous hyperinsulinemic hypoglycemia while fasting is not exclusively caused by insulinomas. Rather than an insulinoma, some individuals have a diffusely expanded islet cell mass. It's frequently called nesidioblastosis, even though the histological finding of islets budding from pancreatic ducts is not always present. Before attempting to localize or regionalize the tumor, there must be strong clinical and biochemical proof that an insulinoma is present.[6] Most insulinomas are found using magnetic resonance imaging (MRI) and computed tomography; however, the success of any one method depends on the centre's knowledge and expertise with that particular technology. Negative imaging cannot, however, rule out the existence of an insulinoma because the diameter of these tumors is often less than 1.0 cm. About 85% are detected by MRI, and 70–80% are using computed tomography.[24] Although a sensitivity of 80% has been documented, somatostatin receptor scintigraphy is known to detect insulinomas in about half of affected patients. Endoscopic pancreatic ultrasonography, which has a sensitivity of over 90%, can be employed, despite being invasive.[25] Preoperative localization of most insulinomas is achieved by a combination of noninvasive and specific invasive modalities, most notably endoscopic ultrasound. Selective pancreatic arterial calcium injections localize insulinomas with high sensitivity; the objective is defined as a larger than 2-fold increase in hepatic venous insulin levels over baseline (or maybe a greater than 5-fold increase with modern specific insulin assays).[26]

This invasive method can aid in the localization of an insulinoma when imaging results are ambiguous or negative. A calcium stimulation test is the recommended method for verifying noninsulinoma pancreatogenous hypoglycemia and post-Roux-en-Y gastric bypass hypoglycemia because conventional imaging is negative in these circumstances. 68 Ga-DOTATE PET/CT is frequently employed to localize insulinoma.[27]

The most frequent causes of hypoglycemia in hospital settings include drugs and renal failure.[28] Inappropriate use of insulin or insulin secretagogues is common, particularly when enteral or parenteral feeding is discontinued or when insulin sensitivity is increased (e.g., after stopping glucocorticoid medication).[10] In critically unwell individuals, hypoglycemia is frequently caused by liver failure, infection, and adrenal insufficiency.

Patients with nonislet cell malignancies frequently experience hypoglycemia due to an excess of partially processed IGF-II;[29] hypoglycemia related to an excess of IGF-I has also been documented.[30] Clinically apparent large mesenchymal tumors are usually associated with hypoglycemia from nonislet cell tumors. Usually, these tumors secrete an excessive amount of pro-IGF-II. Pro-IGF-II to IGF-II ratios may be higher, although overall IGF-II levels may be normal. Low IGF-I levels and decreased GH production lead to an increase in the IGF-II to IGF-I ratio. When nonislet cell malignancies induce hypoglycemia, endogenous insulin secretion is adequately suppressed.[10]

Though the classification of hypoglycemia into fasting and postprandial groups is now abandoned for a new classification, postprandial hypoglycemia still draws much attention in clinical practice. Postprandial hypoglycemia is not a diagnosis in itself; rather, it defines the occurrence of hypoglycemia within four hours following a meal. Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), post-Roux-en-Y gastric bypass (RYGB) hypoglycemia, occult diabetes, and autoimmune hypoglycemia are among the disorders that mostly cause hypoglycemia in the postprandial period.[31]

The term 'postprandial syndrome' refers to a condition that is seen in patients who have postprandial symptoms that may indicate hypoglycemia but do not have concomitant biochemical evidence of hypoglycemia. This condition typically occurs after a high-carb meal is consumed, and symptoms resolve with dietary modification.[32] Since low blood glucose is not thought to be the source of the symptoms, the term 'reactive hypoglycemia,' which was formerly used to characterize this illness, has been abandoned. Anxiety, weakness, tremors, perspiration, palpitations, and other symptoms following meals that suggested a rise in sympathetic activity were previously diagnosed as functional hypoglycemia or functional hyperinsulinism. But in fact, it is the body's overreaction to food rather than an illness. The diagnosis was made based on the patient's symptoms of hypoglycemia being reproduced and a blood glucose level of less than 50 mg/dL (2.8 mmol/L) during an oral glucose tolerance test (OGTT).[33] However, the test does not assist in identifying reactive hypoglycemia because many healthy, asymptomatic individuals have nadir blood glucose concentrations less than 50 mg/dL (2.8 mmol/L) following a four- to six-hour OGTT.[34] Self-monitoring of blood glucose and mixed meal challenge tests are important for the evaluation of postprandial hypoglycemia. Distinguishing between true postprandial hypoglycemic illness and postprandial syndrome is crucial for patients exhibiting signs of hypoglycemia after meals. Continuous glucose monitoring devices should not be used to evaluate spontaneous hypoglycemia.[35] Any low glucose reading on the glucometer should be confirmed by laboratory measurement.

Conclusion

The diagnosis of spontaneous hypoglycemia and its etiology is a challenge for the endocrinologists. Whipple's triad must be fulfilled, and clinical classification of the patient (seemingly well and unwell) is important before embarking on the complicated diagnostic pathway.

Conflict of interest

The authors have no conflicts of interest to disclose.

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