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Review Article

Approach to the patient with spontaneous hypoglycemia

Pieter Martens [a,*], Jos Tits [b]

[a] Department of Internal Medicine, University Hospital Gasthuisberg Leuven, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium
[b] Department of Endocrinology, Hospital Ziekenhuis Oost-Limburg ZOL, Genk, Belgium

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ABSTRACT

Hypoglycemia is common in daily clinical practice and often occurs during the treatment of diabetes mellitus. However, a small minority of hypoglycemia encountered in clinical practice is spontaneous and thus not induced by glycemic lowering agents. These spontaneous hypoglycemic events confront the clinician with a diagnostic enigma. Although the trained clinician can recognize the autonomic and neuroglycopenic symptoms of hypoglycemia even in a patient not on insulin, it remains challenging to decipher the etiology of a spontaneous hypoglycemic event. A logical and stepwise approach to the spontaneous hypoglycemic event allows for a conclusive diagnosis. This diagnostic process consists of adequately diagnosing hypoglycemia by fulfilling Whipple's triad, stratifying patients according to their clinical status and analyzing a full hypoglycemic blood panel. A complete hypoglycemic blood panel should include the analysis of glucose, insulin, C-peptide, pro-insulin, insulin antibodies and the presence of oral hypoglycemic agents. For patients with episodes of hypoglycemia induced by excessive endogenous insulin, additional imaging is often required to detect the presence of an underlying insulinoma. By diagnosing the underlying cause of the spontaneous hypoglycemia, the physician also diagnosis the mechanism by which the hypoglycemic event occurs. Allowing for a problem orientated therapeutic approach.

Methodology: The present review is based upon a comprehensive PubMed search between 1985 and 2013. This uses search terms of spontaneous hypoglycemia, insulinoma, nesidioblastosis, insulin auto-immunity, noninsulinoma pancreatogenous hypoglycemia syndrome, hormone deficiency, pro-IGF II, and pro-insulin growth factor II, and cross reference searching of pivotal articles in the subject.

1. Introduction

In daily clinical practice, hypoglycemia is most commonly iatrogenic, caused by insulin or insulinsecretagogue used to treat diabetes mellitus [1]. The diagnosis and treatment of a hypoglycemic event in a patient using medication to lower plasma glucose level are therefore straightforward. But spontaneous hypoglycemia in a non-diabetic patient confronts the clinician with a diagnostic enigma. Hypoglycemia is confirmed when *Whipple's triad* is present [2,3]: (1) symptoms or signs consistent with hypoglycemia, (2) a plasma glucose level less than 55 mg/dl, measured with a precise method such as a venous blood sample, and (3) resolution of symptoms after raising plasma glucose level [4]. Symptoms consistent with hypoglycemia are broadly categorized as *autonomic* or *neuroglycopenic*. Symptoms that arise first are the autonomic symptoms, mediated by the adrenergic and cholinergic axes of the sympathetic nervous system. Adrenergic symptoms consist of palpitations, tremor, and anxiety and are mediated by an up-regulation of norepinephrine and epinephrine. Cholinergic symptoms include hunger, sweating, and paresthesia and are derived from the acetylcholine released by postganglionic sympathetic neurons. This sympathetic response is part of the physiological counter regulatory mechanism, directed against a decrease in plasma glucose level [4,5]. Although the sympathetic response generates the first type of symptoms, it is not the first counter regulatory mechanism against hypoglycemia. The first physiological response to a decreasing plasma glucose level is a down-regulation of insulin secretion, followed by a second defense of heightened glucagon secretion. Only when these fail to call a halt to the decreasing plasma glucose, is a sympathetic response apparent [6,7]. A second type of symptoms is the neuroglycopenic symptoms. These symptoms arise due to central nervous system glucose deprivation. Neuroglycopenic symptoms range from confusion to amnesia, blurred vision, diplopia, dysarthria, seizure and if sufficiently profound loss of consciousness [8]. Prolonged hypoglycemia can cause brain death and hypoglycemia has shown to increase all-cause mortality in cardiac patients [9,10]. Mortality is especially higher for the spontaneous hypoglycemia in non-diabetics [11]. Probably because the underlying cause heralds a more ominous prognosis and because these hypoglycemic events are a marker for vulnerability. Recurrence of hypoglycemia is a great source of morbidity and generates a great burden to the patient. The following is a discussion on the management of the non-diabetic patient with hypoglycemia.

* Corresponding author at: Department of Internal Medicine, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Tel.: +32 16 34 42 75; fax: +32 16 34 42 30.

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2. Diagnosis of hypoglycemia

Hypoglycemia is uncommon in non-diabetics because of the effectiveness of redundant counter regulatory mechanisms. A rapid decline in insulin secretion combined with an augmented glucagon secretion and heightened sympathetic outflow allows for a rapid response against decreasing plasma glucose levels. Growth hormone and cortisol are implicated in the defense against prolonged hypoglycemia. Only when these defense mechanism fail to substantially increase endogenous glucose mobilization to counter-act the falling glucose levels, does hypoglycemia develop [5,6]. Given the extensive redundancy of these defense mechanisms, one should consider hypoglycemia in non-diabetics a *red flag*. A meticulous evaluation is thus warranted. The diagnostic process starts by the recognition of hypoglycemia as a cause of the presenting symptoms such as confusion, altered level of consciousness, seizure or any of the other autonomic and neuroglycopenic symptoms. This can be difficult because the symptoms are not exclusive for hypoglycemia. Conformation is done by documenting Whipple's triad [4]. After documenting Whipple's triad, two elements are key in the approach to the non-diabetic with hypoglycemia: (1) diagnosis of the hypoglycemic mechanism, and (2) management of the low blood glucose level [4].

3. Mechanism diagnosis

Hypoglycemic disorders used to be classified as being postabsorptive hypoglycemia (fasting hypoglycemia) versus postprandial hypoglycemia (re-active hypoglycemia) [6]. This classification was based on the assumption that the former is caused by organic pathologies presenting mostly with neuroglycopenic symptoms and the latter arises from functional disorder presenting mostly with autonomic features. This classification is not very useful because it neither expedites diagnosis nor facilitates an understanding of the pathophysiology of the disorders causing hypoglycemia [6]. An insulinoma, for example, can present postprandial or a post-absorptive state [12]. A more useful classification for the clinician is to establish whether the patient is *seemingly well* or has a *concurrent illness* [4]. At all times drugs should be suspected, even in the non-diabetic, because insulin or an insulin secretagogue could be administered in an accidental or even malicious fashion. Also some non-antidiabetic drugs can cause an iatrogenic hypoglycemia [13]. The approach of dividing hypoglycemia in categories of seemingly well, concurrent illness or iatrogenic allows for a pathophysiological and therapeutically relevant approach. The different causes of hypoglycemia are listed in Table 1. An initial history, physical examination and careful review of available laboratory information will allow broad categorizing of the different causes of hypoglycemia. Fig. 1 illustrates a proposed diagnostic work-up.

3.1. Concurrent illness

The subgroup concurrent illness defines a group of patients in which the clinical findings during history or physical examination indicate a primary pathology which is held responsible for the hypoglycemic event. Hereby delineating patients at increased risk of mortality in which the hypoglycemic event is a sign of increased vulnerability. Concurrent illnesses that present with hypoglycemia are: critical illnesses, hormone deficiencies and some non-beta cell tumors [4–6].

3.1.1. Critical illnesses

Among hospitalized patients, serious illnesses such as renal, hepatic or cardiac failure, inanition and sepsis are frequent causes of hypoglycemia. Acute and massive hepatocellular injury (e.g. shock liver, toxic hepatitis) abolishes the hepatic ability to increase plasma glucose level by means of glyconeogenesis and induces hypoglycemia typically in a fasting state. Renal failure reduces insulin clearance and diminishes the mobilization of gluconeogenic precursors. The exact mechanism of hypoglycemia in heart failure is unknown. In sepsis there is an increased glucose utilization induced by cytokines [4].

3.1.2. Hormone deficiencies

Growth hormone (GH) and cortisol are implicated in the defense against hypoglycemia during prolonged fasting. Hypopituitarism and primary adrenal insufficiency (Addison's disease) can cause hypoglycemia during prolonged fasts. Chronic cortisol deficiency generates hypoglycemia by inducing a state of precursor deprived gluconeogenesis. Leading to a hypoglycemic event when glycogen storage is depleted. GH deficiency can cause hypoglycemia in children but is uncommon in adults. Both GH and cortisol deficiency lead to a number of symptoms beside hypoglycemia, assisting in the diagnostic process [4,5].

3.1.3. Non-beta cell tumors

Several mesenchymal and epithelial tumors such as hepatomas, gastric tumors or sarcomas can produce an incompletely processed form of insulin-like growth factor II (pro-IGF II). These tumors are mostly large tumors (>10 cm) and generate symptoms not only by means of space occupation, but also by inducing hypoglycemia. Hypoglycemia typically occurs in a fasting state with a typical suppressed insulin concentration by pro-IGF II. This suppressed insulin concentration allows it to be differentiated from hyperinsulinemic states of hypoglycemia. The concentration of IGF II is typically normal, but the ratio of pro-IGF II/IGF II is increased [4,5,14,15].

3.2. Seemingly well

When a patient presents with a spontaneous hypoglycemia, without any apparent stigmata of a causative underlying illness such as critical

Table 1
Causes of hypoglycemia.

Iatrogenic	Concurrent illness	Seemingly well
Insulin or insulinsecretagogue	Critical illness	Endogenous hyperinsulinism
Alcohol	Hepatic, renal, cardiac failure	Insulinoma
Others:	Sepsis	NIPHS/PGBH
Moderate quality of evidence	Inanition	Insulin autoimmunity
Quinine,	Hormone deficiency	Exogenous hyperinsulinism
Gatifloxacin, pentamidine,	Cortisol	Accidental
Indomethacin,	Growth hormone	Factitious
Glucagon (during endoscopy)	Glucagon	Glucagon
Low quality of evidence	Non-beta cell tumors	
Lithium, IGF-I,		
Chloroquinoxaline sulfonamide,		
propoxyphene		
Dextropropoxyphene, Artesunate		

IGF denotes insulin-like growth factor; NIPHS denotes noninsulinoma pancreatogenous hypoglycemia.
PGBH denotes post-gastric bypass hypoglycemia.