MANAGEMENT OF ENDOCRINE DISEASE

Pathogenesis and management of hypoglycemia

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Abstract

Glucose is the main substrate utilized by the brain and as such multiple regulatory mechanisms exist to maintain glucose concentrations. When these mechanisms fail or are defective, hypoglycemia ensues. Due to these robust mechanisms, hypoglycemia is uncommon and usually occurs in the setting of the treatment of diabetes using glucose-lowering agents such as sulfonylureas or insulin. The symptoms of hypoglycemia are non-specific and as such it is important to confirm hypoglycemia by establishing the presence of Whipple’s triad before embarking on an evaluation for hypoglycemia. When possible, evaluation of hypoglycemia should be carried out at the time of spontaneous occurrence of symptoms. If this is not possible then one would want to create the circumstances under which symptoms occur. In cases where symptoms occur in the post absorptive state, a 72-h fast should be performed. Likewise, if symptoms occur after a meal then a mixed meal study may be the test of choice. The causes of endogenous hyperinsulinemic hypoglycemia include insulinoma, post-bariatric hypoglycemia and noninsulinoma pancreaticotogenous hypoglycemia syndrome. Autoimmune hypoglycemia syndrome is clinically and biochemically similar to insulinoma but associated with high levels of insulin antibodies and plasma insulin. Other important causes of hypoglycemia include medications, non-islet cell tumors, hormonal deficiencies, critical illness and factitious hypoglycemia. We provide an overview of the pathogenesis and management of hypoglycemia in these situations.

Introduction

Symptoms of hypoglycemia are common and non-specific. In contrast, hypoglycemia is relatively uncommon and usually occurs in the setting of the treatment of glucose-lowering agents such as sulfonylureas or insulin (1, 2). The diagnosis of hypoglycemia requires fulfillment of Whipple’s triad (3, 4): symptoms, signs or both consistent with hypoglycemia; a low plasma glucose concentration at the time of suspected hypoglycemia; resolution of symptoms or signs when hypoglycemia is corrected. Only after Whipple’s triad is fulfilled should work up for...
hypoglycemia be initiated. This review is intended to provide an overview of the pathogenesis and management of the common causes of hypoglycemia (Table 1).

**Mechanisms of defense against hypoglycemia**

Glucose is an important substrate for the metabolic processes generating energy for homeostasis. It is the main fuel utilized by the brain and as such multiple mechanisms maintain glucose concentrations or alternatively facilitate processes such as lipolysis that generate alternative fuels that can be utilized for cerebral metabolism. It has been shown that the activation of these mechanisms occur at glycemic thresholds that are higher than those at which cognitive impairment occurs (5, 6). The first defense against hypoglycemia is the cessation of insulin secretion from the pancreatic B cells as plasma glucose concentrations decline (7, 8). Decreased insulin secretion appears to occur at a plasma glucose concentration of approximately 81 mg/dL (4.5 mmol/L) (9). The next most important mechanism to prevent hypoglycemia is the increase in glucagon secretion (7). When glucagon production is inadequate, hypoglycemia persists without improvement. Epinephrine is also an important factor in preventing hypoglycemia, but does not appear to be essential in the presence of glucagon. Only when glucagon is deficient or the response is inadequate does the role of epinephrine becomes significant (7). The levels of glucagon and epinephrine increase when glucose concentration falls below the physiologic range (68 mg/dL (3.8 mmol/L)) (9).

In cases of protracted hypoglycemia, cortisol and growth hormones are important counter-regulatory mechanisms; however, in acute hypoglycemia, they do not appear to be significant contributors to the counter-regulatory responses (7). When the above mechanisms fail or are defective, hypoglycemia ensues.

### Table 1 Causes of hypoglycemia.

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**Diagnosis of hypoglycemia**

The symptoms of hypoglycemia can be divided into autonomic and neuroglycopenic (10, 11). Autonomic symptoms occur at plasma glucose concentrations of approximately 60 mg/dL (3.3 mmol/L) whereas neuroglycopenic symptoms occur at plasma glucose concentrations of approximately 50 mg/dL (2.8 mmol/L) or less (5). Autonomic symptoms can further be divided into: adrenergic symptoms that include palpitations, tachycardia, anxiety, tremors; and cholinergic symptoms that include sweating, warmth, nausea and hunger (10). Neuroglycopenic symptoms include weakness, behavioral changes, visual changes, confusion, dysarthria, dizziness/lightheadedness, amnesia, lethargy, seizure, loss of consciousness and coma. Brain death has been known to occur in instances when hypoglycemia is protracted (9).

The presence of autonomic as well as neuroglycopenic symptoms is highly suggestive of hypoglycemia. However, one must note that these symptoms are non-specific. As such it is important to confirm hypoglycemia by establishing the presence of Whipple’s triad before embarking on an evaluation to prevent unwarranted and expensive testing in patients who do not have true clinical hypoglycemia (12). Whipple’s triad (4, 3) consists of: symptoms, signs or both consistent with hypoglycemia; a low plasma glucose concentration at the time of suspected hypoglycemia; resolution of symptoms or signs when hypoglycemia is corrected. It is important that plasma glucose concentrations used to establish and document Whipple’s triad be measured from a venous blood draw and measured in a reliable laboratory (12).

The relationship of hypoglycemia to meals is not important in determining etiology (13). This is because patients with insulinoma may have postabsorptive symptoms, postprandial symptoms or a combination of both (14). Patients with spontaneous plasma glucose concentrations less than 55 mg/dL (3 mmol/L) on
venous blood warrant for further work up. Evaluation of hypoglycemia should be carried out at the time of spontaneous occurrence of symptoms (13). Plasma is obtained for glucose, insulin, C-peptide, pro-insulin, beta-hydroxybutyrate and circulating oral hypoglycemic agents. Once these have been obtained, hypoglycemia is reversed by giving 1 mg of glucagon intravenously and plasma glucose is measured. Diagnostic values for endogenous hyperinsulinemia are a plasma insulin concentration of at least 3 μU/mL (18 pmol/L), plasma C-peptide concentration of at least 0.6 ng/mL (0.2 nmol/L), proinsulin concentration of at least 5.0 pmol/L, beta hydroxybutyrate <2.7 mmol/L when the fasting plasma glucose is less than 55 mg/dL (3 mmol/L) (12). If spontaneous symptoms do not occur then one would want to recreate the circumstances under which symptoms occur.

The main aim of the supervised 72-h fast is to confirm hypoglycemia as a cause of the patient’s symptoms and to endeavor to determine the cause/ etiology of hypoglycemia. Hirshberg et al. showed that 43% of patients undergoing a supervised fast will become hypoglycemic and symptomatic in 12 h, 67% within 24 h, 95% within 48 h and 100% within 72 h (15).

The fast can be initiated during outside office hours but needs to be completed, when necessary, in an inpatient facility. The onset of the fast is set at the last prior meal and ingestion of calories (16). During the fast, the patient is allowed to have non-caloric and caffeine-free beverages (16). Non-crucial medications are discontinued and patients are advised to continue their normal activity while awake (16). Plasma glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate are obtained every 6 h till the blood glucose concentration drops to 60 mg/dL (3.3 mmol/L) or less at which point they are obtained every 1–2 h. The fast is concluded once the patient has symptoms and plasma glucose concentration is 45 mg/dL (2.5 mmol/L) or less or after 72 h if the patient has had no symptoms or signs of hypoglycemia or decreased plasma glucose concentrations as described above (16). Once the fast is concluded, plasma concentrations of glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate and circulating oral hypoglycemic agents are measured and 1 mg of glucagon is given intravenously (16). Plasma glucose concentrations are then measured at 10, 20 and 30 min after injection. In cases of hyperinsulinemic hypoglycemia due to an insulinoma, an increase of glucose ≥25 mg/dL (1.4 mmol/L) is expected. This is because increased insulin concentrations inhibit hepatic glycogenolysis with preservation of hepatic glycogen stores. Administration of glucagon will cause mobilization and release of glucose from preserved hepatic glycogen stores. Once this has been done, the patient is fed.

In contrast, in cases where the history obtained suggests that symptoms occur after meals, indicative of possible postprandial hypoglycemia, a mixed meal study may be the test of choice. This is performed after an overnight fast. Patients are given a meal similar to what provokes their symptoms. In patients who have altered upper gastrointestinal anatomy, such as patients who have undergone a Roux-en-Y gastric bypass, a standardized meal is required with no calories in liquid form. Plasma glucose, insulin, C-peptide, proinsulin and are obtained at baseline and then every 30 min for 5 h. It is important to note that an oral glucose tolerance test has no role in the evaluation of hypoglycemia (17). This is because approximately 10% of healthy people can have a plasma glucose of less than 50 mg/dL (2.8 mmol/L) during an oral glucose tolerance test (18). During the evaluation of hypoglycemia, it is essential to test for insulin antibodies and (at the time of hypoglycemia) screen for oral hypoglycemic agents (insulin secretagogues) to rule out insulin autoimmune hypoglycemia syndrome and hypoglycemia caused by oral hypoglycemic agents respectively.

**Insulinoma**

Insulinoma (Fig. 1) is the most common functioning neuroendocrine tumor of the pancreas, first described in 1927 (19). According to a population-based study, it occurs with an incidence of 4 per million patient years (20). It is characterized by endogenous hyperinsulinemic hypoglycemia with an inappropriate insulin concentration for the prevailing plasma glucose concentration. Localization studies are carried out once there is convincing biochemical evidence to support hyperinsulinemic hypoglycemia.

Imaging is essential to locate the tumor, determine the extent of the disease and evaluate for the presence of metastases. Non-invasive imaging includes computed tomography, MRI and transabdominal ultrasonography (21, 22). Invasive techniques include somatostatin receptor scintigraphy, endoscopic pancreatic ultrasound with fine-needle aspiration, transhepatic portal venous sampling, selective angiography and selective pancreatic arterial calcium stimulation (21, 23). More recently PET/CT with 68Ga-DOTA-exendin-4 has been used to localize insulinoma (24, 25). Surgical exploration is carried out once the diagnosis of hypoglycemia has been confirmed and tumor enucleation is the mainstay of therapy (21).
Laparoscopic procedures have been used in many instances (26, 27, 28, 29). Medical management including the use of diazoxide, long-acting somatostatin analogs such as octreotide and lanreotide, and ethanol ablation have been used (21, 30) in patients who are not candidates for surgical therapy.

**Post bariatric hypoglycemia**

Hypoglycemia is a known complication of Roux-en-Y gastric bypass (RYGB) (Fig. 1) and other procedures which bypass the pylorus, or alter upper gastrointestinal function. The prevalence of post-RYGB hypoglycemia is uncertain but has been estimated to occur in 0.2–1% of patients (31) and appears to be more common in women than in men. The time of onset of symptoms after surgery is variable but patients typically present with postprandial symptoms. The pathogenesis of this disorder is uncertain.

The condition rose to prominence after the study by Service et al. described 6 patients with endogenous hyperinsulinemic hypoglycemia following RYGB (32) who underwent partial pancreatectomy to control their symptoms. Pathological examinations of the surgical specimen suggested appearances compatible with nesidioblastosis. Subsequently, the study by Patti et al. described 3 patients with a similar presentation who also underwent partial pancreatectomy and exhibited similar pathology (33). In contrast, the study by Meier et al. did not find evidence of islet cell hyperplasia when they examined the specimens of the patients described previously (32) as having nesidioblastosis (34), merely an increase in the nuclear diameter of the beta cells when compared to autopsy specimen (34). This disparity in conclusions might arise from the controls used – it has been argued, for example that post-mortem autolysis might alter cellular size in autopsy specimen – and the lack of a clear definition of what constitutes abnormal histology after RYGB.

Given the effects of RYGB on glucose metabolism and the amelioration of type 2 DM (35, 36), there have been suggestions that this condition may represent an excessive and aberrant response to bariatric surgery e.g. caused by excess secretion of glucagon-like peptide-1 (GLP-1) (37, 38). There are significant theoretical objections to this hypothesis (39) and ultimately, GLP-1 plays a small role in glucose disposal after RYGB (40, 41). However, the study by Salehi et al. have demonstrated that competitive antagonism of the GLP-1 receptor can ameliorate the post-prandial glucose nadir in affected patients (42, 43).

The first line of therapy in patients with post bariatric bypass hypoglycemia is dietary modification as demonstrated in the study by Kellogg et al. (44), who studied 14 patients with hyperinsulinemic hypoglycemia. These patients were given a mixed meal high in carbohydrates on day 1 and a meal low in carbohydrates on day 2. Plasma glucose and insulin concentrations were measured at baseline and then at 30-min interval after meal ingestion. Twelve of 14 patients developed hyperglycemia during the high carbohydrate meal. When the same subjects consumed a low carbohydrate diet, hypoglycemia was ameliorated. The investigators concluded that a low carbohydrate diet was less likely to

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**Figure 1**

Mechanisms of the pathogenesis of hypoglycemia in various situations. The (+) lines represent a stimulatory effect, the (−) lines represent an inhibitory effect.
cause hypoglycemia and improved symptoms in these patients (44).

When dietary interventions do not alleviate symptoms, α-glucosidase inhibitors have been utilized. These compounds decrease the postprandial rise in glucose and insulin but their use is limited by adverse effects of flatulence and diarrhea. Analogs of somatostatin such as octreotide and lanreotide have been used to treat post-RYGB hypoglycemia when dietary interventions and α-glucosidase inhibitors are ineffective (45). These compounds inhibit insulin secretion and decrease bowel motility and postprandial splanchnic vasodilation ameliorate postprandial symptoms. In some instances, diazoxide that is used in the treatment of hypertension and insulinoma have been used (46). Unfortunately, there is a dearth of studies which have rigorously examined the longitudinal effect of therapy on post-RYGB hypoglycemia.

Pancreatectomy has been used for the treatment of post-RYGB hypoglycemia (32, 33). Mathavan et al. retrospectively studied 15 patients who had post bypass hypoglycemia (47). Nine underwent surgery involving extended distal pancreatectomy (eight had laparoscopic surgery and one had a conversion of laparoscopic surgery to open surgery). All of the nine patients had resolution of their symptoms after the surgery initially; however, 77% developed recurrence in their symptoms (47). The study by Alvarez et al. described a laparoscopic spleen-preserving distal pancreatectomy in a patient with post-RYGB hypoglycemia who remained free of symptoms at 10 months (48). The extent of pancreatic resection differs in the literature with Mathavan describing pancreatic resection of 80% of the parenchyma in eight of nine patients (47), the study by Thompson et al. described pancreatic resection of 80% (49) and the study by Harness et al. described pancreatic resection of up to 50–100% (50).

However, Vanderveen et al. studied 75 patients who had undergone partial pancreatectomy for hypoglycemia (51). The majority of the patients (64%) had a history of prior bariatric surgery. Forty-one (87%) patients had recurrent symptoms after partial pancreatectomy with one patient requiring total pancreatectomy for severe and persistent symptoms (51). As the majority of patients continue to have symptoms after partial pancreatectomy, this procedure has been largely abandoned for the treatment of post-RYGB hypoglycemia.

The case reports have suggested that continuous enteral feeding (52) by insertion of a gastrostomy tube into the remnant stomach alleviates symptoms of hypoglycemia. In refractory cases of post-RYGB hypoglycemia, reversal of the RYGB has been described. The study by Himpens et al. first described the reversal in a patient with severe dumping syndrome without hypoglycemia (53). In a more recent series (54), reversal was performed in three patients with refractory hyperinsulinemic hypoglycemia and neuroglycopenia. At a mean follow-up of 12 months (range 3–22 months), there were no further episodes of neuroglycopenia and the number of hypoglycemic events per week decreased. This suggests that reversal of RYGB may be a reasonable therapeutic option in patients with severe refractory symptoms of hypoglycemia.

**Non-insulinoma pancreatogenous hypoglycemia syndrome**

Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) (Fig. 1) is a rare condition first described in the study by Service et al. in 1999 (55). It is often confused with post bypass hypoglycemia; however patients with NIPHS do not have a history of gastric bypass surgery. Imaging of the pancreas with studies such as trans-abdominal ultrasound, abdominal CT, MRI, EUS and intraoperative ultrasound are negative (49, 55). Thus, NIPHS should be considered in patients who do not have a history of gastric bypass and present with endogenous hyperinsulinemic hypoglycemia in the setting of a negative localizing imaging studies. Hypoglycemia typically occurs in the postprandial period.

Surgical specimens exhibit features of nesidioblastosis (55). Imaging was negative for insulinoma. However, no genetic mutation (KCNJ11 and ABCC8) associated with congenital nesidioblastosis was detected in these patients (55).

Diagnosis usually requires selective arterial calcium stimulation with hepatic vein sampling in which the insulin response is positive in multiple vascular territories of the pancreas (49, 55, 56).

Diaxoxide has been used to manage NIPHS in some cases (57). In severely symptomatic patients or patients with refractory symptoms, distal pancreatectomy is the recommended treatment of choice (49, 55).

**Insulin autoimmune hypoglycemia syndrome**

Insulin autoimmune hypoglycemia syndrome was first described as a cause of hypoglycemia by Hirata in 1972 (58). This is clinically and biochemically similar to the presentation of hypoglycemia caused by insulinoma but for the presence of insulin antibodies and plasma insulin.
It will however not always be practical to avoid prescribing medications that may cause hypoglycemia. Caution must be taken in prescribing potential offenders to patients with liver and renal diseases. Treatment of drug-induced hypoglycemia usually involves cessation of the offending drug and reversing acute hypoglycemia. This can be done orally in patients who are conscious and do not have severe symptoms with 15 g of glucose. In patients who cannot take oral glucose or have severe hypoglycemia, then correction with 50% dextrose or glucagon is warranted. An infusion of 10% dextrose at 100 mL/h is then used to maintain blood glucose levels and may be needed for several hours as premature discontinuation may result in further hypoglycemic episodes.

**Non-islet cell tumors**

In rare cases, recurrent hypoglycemia may occur in patients with benign or malignant solid tumors of mesenchymal, epithelial, hematopoietic and rarely neuroendocrine origin as a paraneoplastic syndrome (79, 80). These tumors express high molecular weight IGF2 (‘Big’ IGF2), which is an incompletely processed posttranslational precursor of IGF2 (81, 82). IGF2 is similar in structure to insulin and stimulates the insulin receptor (Fig. 1). As such ‘Big’ IGF2 binds to the insulin receptor and IGF receptors. This results in decreased glucose production from the liver and increased uptake of glucose from the systemic circulation by muscles and peripheral tissues with resultant hypoglycemia. Hypoglycemia in non-islet cell tumors usually occurs in the postabsorptive phase and is characterized by hypoinsulinemia with low blood glucose, low insulin, low C-peptide levels and suppressed beta-hydroxybutyrate (83). Growth hormone, IGF1 (83) and IGFBP3 are also low (84). There is a normal response to glucagon as glycogenolysis is inhibited by the insulin-like actions of ‘Big’ IGF2. As discussed above, ‘Big’ IGF2 levels are high. An IGF2:IGF1 ratio of 10 or more is diagnostic (80, 85). Other mechanisms for hypoglycemia caused by non-islet cell tumors include decreased production of glucose from the liver due to infiltration of the liver by tumor. Large tumor bulk is often seen in cases of tumors that cause hypoglycemia. Hypoglycemia in some cases is the first presenting symptom of malignancy (80) and workup for hypoglycemia invariably leads to the diagnosis of malignancy.

As in other cases of hypoglycemia discussed above, management of acute hypoglycemia involves the administration of intravenous dextrose. Glucagon can be given in severe cases (86). Encouraging patients to eat frequent carbohydrate snacks can also help in reducing frequency and symptoms of hypoglycemia. In some
instances, total parenteral nutrition may be needed (87). Complete resection of the tumor if possible, is curative (81). Debulking of large tumors that cannot be completely resected may also reduce hypoglycemic episodes. Embolization has also been carried out in cases where the tumor is unresectable (88, 89, 90). Radiotherapy and chemotherapy may also be needed to decrease tumor burden and subsequently limit episodes of hypoglycemia. For cases in which complete resection of the tumor is not possible, medications may be used to control hypoglycemia. Diaxoxide has been used in the treatment of hypoglycemia in non-islet cell tumors though with limited success (91, 92). Somatostatin analogs have been used with success in some cases (93). However, in other cases there has been no improvement in blood glucose likely due to the fact that the tumors do not have somatostatin receptors or lack functional somatostatin receptors (93, 94). Glucocorticoids and growth hormones have been also been used alone or in combination in the management of hypoglycemia mediated by non-islet cell tumors (94, 95, 96, 97, 98, 99). Cost may limit the long-term use of growth hormone and there is the concern for potential tumor growth caused by GH (87). There have been reports of use of imatinib in cases of non-islet cell tumor hypoglycemia with some success (100).

Sepsis and hypoglycemia

In critically ill patients, decreased glycogen stores, impaired gluconeogenesis and increased peripheral glucose utilization predispose to hypoglycemia (101, 102). Critical illness increases physical stress. Relative or absolute adrenal insufficiency has many potential etiologies including medications such as etomidate that interferes with corticosteroid synthesis (103, 104). Patients who are septic or have thrombocytopenia from a variety of causes are at risk of bilateral adrenal hemorrhage or infarction resulting in adrenal insufficiency (105). Hypoglycemia can be a part of the presentation in critical illness but is rarely prominent and should be sought and treated in such situations as hypoglycemia in critical illness has been associated with increased mortality (106, 107, 108).

Hypoglycemia in adrenal insufficiency

Cortisol has an important role in the counter-regulatory mechanisms that protect against hypoglycemia. It impairs insulin signaling, increases gluconeogenesis, lipolysis, ketogenesis, proteolysis and decreases glucose utilization. The commonest cause of primary adrenal insufficiency is autoimmune disease in developed countries (109); however in developing countries infections such as tuberculosis are an important cause of primary adrenal insufficiency (110). Other causes of primary adrenal insufficiency may be due to adrenal hemorrhage (105) or infarction. Secondary and tertiary adrenal insufficiencies are due to disorders of the pituitary and hypothalamus respectively.

Hypoglycemia in adult patients with primary adrenal insufficiency is uncommon, although patients with Addison’s disease are at increased risk of hypoglycemia. The study by Christiansen et al. demonstrated that acute withdrawal of cortisol increased insulin sensitivity close to 70%, increased glucose oxidation by 50%, with decreased endogenous glucose production, implying that adrenocortical failure could result in hypoglycemia (111). Meyer et al. studied 13 patients with primary adrenal insufficiency using continuous glucose monitoring for 3–5 days (112). One patient was detected to have nocturnal hypoglycemia with a blood glucose concentration of less than 50mg/dL. When the patient’s last hydrocortisone dosing was changed to late evening, there were no further episodes of hypoglycemia (112).

Hypoglycemia is encountered more in patients with secondary adrenal insufficiency and is also seen in young children with hypopituitarism. The treatment involves replacement with a physiological dose of oral corticosteroids split twice or three times daily (113) and in cases of adrenal crises high-dose intravenous hydrocortisone is given (114). Immediate correction of hypoglycemia is done using intravenous dextrose.

Factitious hypoglycemia

Factitious hypoglycemia may be challenging to prove and requires a detailed history to prove access to glucose-lowering medications, and, ideally a drug screen that is positive at the time of hypoglycemia. Factitious hypoglycemia is usually due to the surreptitious use of insulin or insulin secretagogues such as sulfonylureas and meglitinides (16, 115, 116, 117, 118). In cases involving older patients it may be due to inadvertent use of a partner’s oral hypoglycemic agent or a dispensing error (119). Treatment in these cases involves cessation of the offending medication, reversal of hypoglycemia acutely with 50% dextrose, or glucagon and subsequent dextrose infusion to maintain normal blood sugars. Occasionally, (in hypoglycemia caused by an insulin secretagogue) a somatostatin infusion may be required.
Conclusion

Hypoglycemia is a common phenomenon in the setting of treatment of diabetes with glucose-lowering medications. There are however uncommon causes of hypoglycemia which cause significant morbidity. Before the evaluation of hypoglycemia, it is important to establish that true hypoglycemia exists by fulfilling Whipple’s triad. Treatment of acute hypoglycemia is important to prevent sequelae of prolonged hypoglycemia that may result in irreversible neurological sequelae.

Declaration of interest

Dr Vella is a local PI in a multicenter study of post-RYGB hypoglycemia sponsored by XOMA pharmaceuticals, Berkeley, CA, USA.

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