



Refractory hypoglycemia in a patient with functional adrenal cortical carcinoma

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Summary

Adrenocarcinomas are rare, and hypoglycemic syndrome resulting from the secretion of insulin-like growth factor II (IGF-II) by these tumors have been described infrequently. This study describes the case of a young woman with severe persistent hypoglycemia and a large adrenal tumor and discusses the physiopathological mechanisms involved in hypoglycemia. The case is described as a 21-year-old woman who presented with 8 months of general symptoms and, in the preceding 3 months, with episodes of mental confusion and visual blurring secondary to hypoglycemia. A functional assessment of the adrenal cortex revealed ACTH-independent hypercortisolism and hyperandrogenism. Hypoglycemia, hypoinsulinemia, low C-peptide and no ketones were also detected. An evaluation of the GH-IGF axis revealed GH blockade (0.03; reference: up to 4.4 ng/mL), greatly reduced IGF-I levels (9.0 ng/mL; reference: 180–780 ng/mL), slightly reduced IGF-II levels (197 ng/mL; reference: 267–616 ng/mL) and an elevated IGF-II/IGF-I ratio (21.9; reference: ~3). CT scan revealed a large expansive mass in the right adrenal gland and pulmonary and liver metastases. During hospitalization, the patient experienced frequent difficult-to-control hypoglycemia and hypokalemia episodes. Octreotide was ineffective in controlling hypoglycemia. Due to unresectability, chemotherapy was tried, but after 3 months, the patient's condition worsened and progressed to death. In conclusion, our patient presented with a functional adrenal cortical carcinoma, with hyperandrogenism associated with hypoinsulinemic hypoglycemia and blockage of the GH-IGF-I axis. Patient's data suggested a diagnosis of hypoglycemia induced by an IGF-II or a large IGF-II-producing tumor (low levels of GH, greatly decreased IGF-I, slightly decreased IGF-II and an elevated IGF-II/IGF-I ratio).

Learning points:

- Hypoglycemia syndrome resulting from the secretion of insulin-like growth factor II (IGF-II) by adrenal tumors is a rare condition.
- Hypoinsulinemic hypoglycemia associated with hyperandrogenism and blockage of the GH-IGF-I axis suggests hypoglycemia induced by an IGF-II or a large IGF-II-producing tumor.
- Hypoglycemia in cases of NICTH should be treated with glucocorticoids, glucagon, somatostatin analogs and hGH.

Background

This paper describes an unusual presentation of a patient with a functional adrenal cortical carcinoma, with hyperandrogenism associated with hypoinsulinemic hypoglycemia and blockage of the GH-IGF-I axis.

Patient's data suggested a diagnosis of hypoglycemia induced by an IGF-II or a large IGF-II-producing tumor (low levels of GH, greatly decreased IGF-I, slightly decreased IGF-II and an elevated IGF-II/IGF-I ratio).





Table 1 Measurements of blood glucose levels at baseline, after infusion of the glucose suspension and after the administration of glucagon to correct hypoglycemia.

Time point	Blood glucose (70–99 mg/dL)	Insulin (2.6–24.9 µm/mL)	C-peptide (1.1–4.4 ng/mL)	Ketone (mmol/L)
Basal	60	<0.6	0.5	0.1
Suspension of glucose solution				
60 min	33	<0.6	<0.3	0.1
Intravenous administration of glucagon				
20 min	69	–	–	–
20 min	98 (+65)	–	–	–
30 min	87	–	–	–

Case presentation

A 21-year-old black woman had presented 8 months prior to the described events with bloating, weakness, lack of appetite, nausea, weight loss, dyspnea and edema of the lower limbs. In the preceding 3 months, her general condition had worsened, and she experienced episodes of mental confusion and visual blurring secondary to glycemia of approximately 30 mg/dL. Initial findings included BP of 150/90 mmHg, HR 126 bpm, weight 72 kg, height 164 cm, BMI 26.8 kg/m², diffuse xerosis, cushingoid facies, acne in the frontal and chest regions, hyperchromic spots in the frontal region, increased facial and chest hair and grade 2 cervical acanthosis. There was an absence of buffalo hump, swelling of the supraclavicular fossa, abdominal striae and skin bruising. A mass of stony consistency was detected on the patient's right side.

Investigation

An overall laboratory assessment produced the following findings: 13,920 leukocytes/mL (72.0% neutrophils and 0% eosinophils); Na=141 mEq/L (135–145 mEq/L); K=2.7 mEq/L (3.5–5 mEq/L); serum albumin=2.5 g/dL (3.4–4.8 g/dL); gamma-glutamyl transferase (GGT)=212 U/L (5–36 U/L) and metabolic alkalosis (pH=7.56 and bicarbonate=32 mmol/L). A functional assessment of the adrenal cortex revealed ACTH-independent hypercortisolism and hyperandrogenism (serum cortisol=44.2 (5–25 µg/dL); urinary cortisol=1.097 (50–310 µg/24 h); salivary cortisol at 24 h=0.93 (<0.12 µg/dL); androstenedione=3.14 (<2.2 ng/mL); testosterone=106 (<48 ng/dL); dehydroepiandrosterone sulfate=5.920 (1.480–4.870 ng/mL); adrenocorticotrophic hormone <2 (7.2–63.3 pg/mL)). A hypoglycemia assessment conducted an hour after the infusion of a 50% glucose suspension revealed glucose of 33 mg/dL, insulin <0.6 U/mL, C-peptide <0.3 mg/mL and no ketones;

hypoglycemia was corrected via the administration of glucagon (Table 1). An evaluation of the GH-IGF axis revealed GH blockade (0.03; reference, up to 4.4 ng/mL), greatly reduced IGF-I levels (9.0 ng/mL; reference, 180–780 ng/mL), slightly reduced IGF-II levels (197 ng/mL; reference, 267–616 ng/mL) and an elevated IGF-II/IGF-I ratio (21.9; reference, ~3).

An abdominal CT scan revealed a large, heterogeneous expansive mass in the right adrenal gland (15.0×15.0×14.0 cm³) that was in contact with the right kidney and the right liver lobe, with no signs of invasion. The liver was increased in size, with multiple hypervascularized nodules (Fig. 1). A chest CT scan revealed multiple bilateral pulmonary nodules compatible with metastases.

A liver biopsy permitted a diagnosis of a poorly differentiated carcinoma, with an immunohistochemical profile compatible with adrenal cortical carcinoma (negative for cytokeratin 7, Hep Par 1, 35BH11, PAX-8, TTF-1 and chromogranin but positive for inhibin and vimentin).

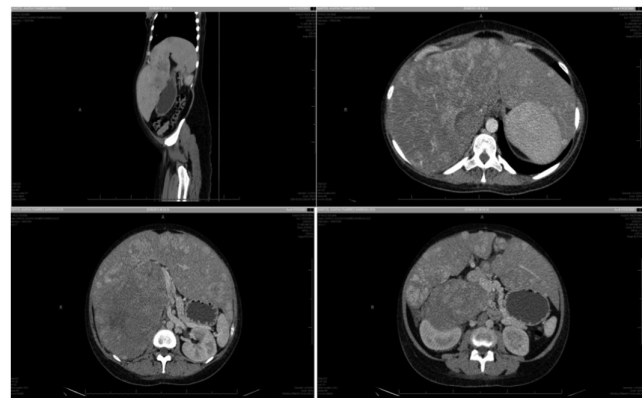


Figure 1
CT scans of the abdomen and pelvis, revealing a large mass on the right adrenal gland (arrow) and multiple liver nodules suggestive of secondary lesions.



Treatment

During hospitalization, the patient experienced frequent hypoglycemic episodes and exhibited difficult-to-control hypokalemia despite the intravenous administration of potassium and hypertonic glucose. The introduction of octreotide was ineffective at controlling hypoglycemia. A combination of enalapril, spironolactone, amlodipine and hydralazine was required to control hypertension. Due to the unresectability of her tumor, the patient underwent 2 cycles of chemotherapy. The first cycle included cisplatin, etoposide, doxorubicin, and mitotane, whereas the second cycle involved cisplatin; no response to either regimen was observed. After 3 months, the patient's condition worsened and progressed to death.

Outcome and follow-up

No response to either chemotherapy regimen was observed. After 3 months, the patient's condition worsened and progressed to death.

Discussion

Hypoglycemia in non-diabetic patients may be attributable to the hypersecretion of insulin or related peptides, a lack of counter-regulatory hormones, the failure of organs involved in the endogenous production of glucose or serious diseases. Noninsulinoma tumor-associated hypoglycemia can be secondary to neoplasms that produce IGF-II or big IGF-II, also known as non-islet-cell tumors (NICTHs) or IGF-II-omas (1, 2, 3, 4). Such neoplasms are generally solid tumors of unknown prevalence, although they are rarer than insulinomas. Among NICTH, 45%, 23%, 10% and 8% are mesenchymal, hepatic, adrenal, and gastrointestinal respectively. Relatively rarely, NICTHs have been described in cases involving leukemia, lymphoma and/or pheochromocytoma (3).

In normal individuals, most of the circulating IGF-II is in the form of a 7.5 kDa peptide. In patients with NICTH, a higher percentage of IGF-II can circulate as a precursor of an 11–18 kDa molecule known as big IGF-II (5). IGF-II has insulin-like effects, and its interaction with insulin receptors increases glucose uptake in muscles and decreases liver glycogenolysis and neoglucogenesis, causing hypoglycemia. In fatty tissue, lipolysis is decreased, leading to the increased supply of fatty acids and glycerol, known substrates of ketogenesis and neoglucogenesis, resulting in glycogen accumulation and the worsening of hypoglycemia. Blockage of the pancreatic secretion

of insulin and glucagon is also observed. Normally, the binding of IGF-II to plasma proteins prevents this factor from passing through the capillary barrier and therefore precludes the aforementioned effects. However, because big IGF-II does not bind correctly to protein carriers, it easily crosses the capillary barrier and fully exerts its insulin-like effects (4, 5). Therefore, in NICTH, the hypoglycemia is associated with low insulin levels but blocked ketones and positive responses to glucagon (6). The effects of big IGF-II on the insulin receptor also promote the intravascular to intracellular transport of potassium (7).

When interacting with IGF-I receptors, IGF-II blocks the pituitary secretion of GH, decreasing the production of IGF-I by the liver. This change in the GH-IGF axis increases sensitivity to insulin and decreases the levels of IGF carrier proteins, increasing the availability of free IGF-II, expanding its hypoglycemic effects and potentially leading to hypokalemia. Thus, patients with NICTH have hypoglycemia with hypoinsulinemia, low C-peptide levels, decreased IGF-I and variable IGF-II, with an elevated IGF-II/IGF-I ratio (7).

A multicenter prospective observational study that included 78 patients from 67 centers described the characteristics of NICTH (7). The most frequent initial manifestation was weight loss associated with an abdominal mass and pain (52%), followed by hypoglycemia (48%). In this study, 30%, 12% and 7% of NICTH were hepatocarcinomas, gastric carcinomas and mesotheliomas respectively (with adrenal tumors accounting for 1.2% of the NICTH). All patients presented with low IGF-I; 39% of patients were positive for big IGF-II (42% exhibited increased free IGF-II and 93% of these patients had an elevated IGF-II/IGF-I ratio). In 90%, serum insulin was $<6 \mu\text{g/mL}$. Hypoglycemia associated with hypokalemia occurred in 53% of cases. There was a significant reduction in big IGF-II and the resolution of hypoglycemia after tumor resection. Thus, it can be concluded that in the diagnosis of NICTH, the suppression of IGF-I and an increase in the IGF-II/IGF-I ratio are more important than the detection of elevated big IGF-II (7).

Our patient presented with a functional adrenal cortical carcinoma, with Cushing's syndrome and hyperandrogenism associated with hypoinsulinemic hypoglycemia and blockage of the GH-IGF-I axis. The data suggest a diagnosis of hypoglycemia induced by an IGF-II- or big IGF-II-producing tumor (low levels of GH, greatly decreased IGF-I, slightly decreased IGF-II and an elevated IGF-II/IGF-I ratio). Because the tumor was unresectable, pharmacological treatment was administered. The hypoglycemia in cases of NICTH



is treated with glucocorticoids (8) or with glucagon (9), somatostatin analogs and hGH (9). Due to the hypercortisolism, somatostatin analog was administered, although unsuccessfully, followed by chemotherapy treatment, which also produced no response.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors have assisted the patient during admission. Katia Regina Marchetti made the first draft and all the other authors made suggestions to improve the text. Edison Ferreira Paiva assisted with the final version.

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