

Hypoglycemia related to big Haemangiopericitoma: a difficult diagnostic definition

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Summary. We describe the case of a 91 years old woman admitted to our department for dyspnea associated with drowsiness. At the admission to the Emergency Room the patient stay in a comatose state and blood tests performed showing severe hypoglycemia (38 mg/dl at admission in non diabetic patient). Anamnestic history: multifactorial anemia; frequent hospitalizations for heart failure; AMI treated with stenting; in 1986 Haemangiopericytoma resection in the right iliac region; in 2006 palliative surgery for recurrence with residual mass. Blood tests showed lower levels of insulin and normal C- peptide serum concentration in correspondence of low glucose concentration (in relation to continuous and adequate parenteral nutrition), IGF 1 and GH level was respectively suppressed (IGF1=47 ng/ml whit normal range 97-331 ng/ml) and normal/low (GH 0.43 uUI/mL whit normal range 0.06-14.00 uUI/mL). Therefore hypoglycemia appeared related to paraneoplastic production of IGF -2. (www.actabiomedica.it)

Key words: hypoglycemia, Haemangiopericitoma, IGF-1

Background

Hypoglycemia is a complication that usually occurs in diabetic patients. This condition is more common in patients with type I diabetes and is relatively less frequent in patients with type II diabetes. In not diabetic patients this condition is rare (1) and can be associated with the presence of neoplasm. Tumors can make hypoglycemia are divided into Non-Islet cell tumor and Islet cell tumor.

Non islet cell tumor hypoglycemia is a rare complication of benign and malign tumors. This condition was discovered around the 1970 when the first cases were described. In this period was supposed that this syndrome was related to the increased glucose utilization by large tumor. The true mechanism trough non islet cell tumor produced hypoglycemia was described in 1980-1990 period when a new peptide implicated in the pathogenesis was isolated: the "big-IGF

II". Not islet cell tumors hypoglycemia (NICTH) is a rare complication that develops when some tumors produce an incomplete and large IGF2 which is released into the plasma and it is free to binds and stimulates insulin receptors. In addition some authors have proposed an autoimmune mechanism to explain paraneoplastic hypoglycemia. Only a few types of tumors can produce this complication such as mesenchymal tumors, carcinoid, myeloma, lymphoma, hepatocellular tumors and colon carcinoma (2). There are typically large tumors that often weigh 2-4 kilograms and are located in the chest in a third of cases and in the retroperitoneal region in two thirds of cases.

Case presentation

We describe the case of a 91 years old woman admitted to our department for dyspnea associated with

drowsiness. At the admission to the Emergency Room the patient stay in a comatose state and blood tests performed showing severe hypoglycemia (38 mg/dL) in non-diabetic patient (Table 1). Gas Analysis: pH 7.27, pCO₂ 46 mmHg, pO₂ 56 mmHg, HCO₃-20 mmol/L, lactate 0.6 mmol/l. The patient was treated with 4 vials of glucose 33%, followed by glucose 5% and transferred to our Unit.

Anamnestic history: multifactorial anemia; frequent hospitalizations for heart failure; AMI treated with stenting; in 1986 Hemangiopericytoma resection in the right iliac region; in 2006 palliative surgery for recurrence with residual mass; the patient wasn't diabetic and doesn't take oral hypoglycemic drugs. At admission was maintained infusion with 10% glucose and after, in consideration of comatose state, we infused continuous parenteral nutrition.

Investigation

To investigate the genesis of hypoglycemia (38 mg/dl at admission in non diabetic patient) were per-

formed both laboratory and instrumental investigations; especially: blood tests showed lower levels of insulin and normal C-peptide serum concentration in correspondence of low glucose concentration (in relation to continuous and adequate parenteral nutrition) Table 2; a total body PET showed a nonspecific hypermetabolism in pancreatic area in the absence of other areas of altered distribution of the tracer; abdominal ultrasound echograph and x-ray chest were also negative for new neoplastic lesions.

To investigate a possible paraneoplastic hypoglycemia we perform IGF1 and GH serum dosage. In view of general state of patient parenteral nutrition was maintained. IGF 1 and GH level was respectively suppressed (IGF1=47 ng/ml whit normal range 97-331 ng/ml) and normal/low (GH 0.43 uUI/mL whit normal range 0.06-14.00 uUI/mL).

Therefore hypoglycemia appeared related to paraneoplastic production of IGF-2. Some cancers (most commonly malignant tumors of mesenchymal origin, tumors of vascular origin such as Hemangiopericytoma, and epithelial tumors) may synthesize a large, incomplete IGF-2 peptide which is not bound by the

Table 1. Blood tests to admission in emergency room

Blood tests to admission in emergency room	Patient values	Normal values
WBC	7100/mm ³	4000-10 000
RBC	3 090 000/mm ³	3900000-5200000
HB	9.5 g/dl	12-16
HT	31.2%	36-46
PLT	170 000/mm ³	150-400
INR	1.09	0.86-1.14
Glucose	38 mg/dl	60-100
BUN	254 mg/dl	10-50
Creatinine	1.9 mg/dl	0.5-1.4
Transaminases (GPT)	6 U/L	0-40
Sodium	140 mEq/L	135-148
Potassium	4.5 mEq/L	3.5-5.3
CK	3.2 ng/mL	0.0-4.0
Troponin	0.10 ng/mL	0.01-0.06

Table 2. Laboratory data after 4 days of continuous parenteral nutrition

Laboratory data after 4 days of continuous parenteral nutrition	During parenteral nutrition	Normal value
Glycated emoglobin	29 mmol/mol	19-43
Glucose	62 mg/dl	60-100
Insulin	1 uU/mL	3-16
C-Peptide	4.57 ng/mL	0.80-4.20

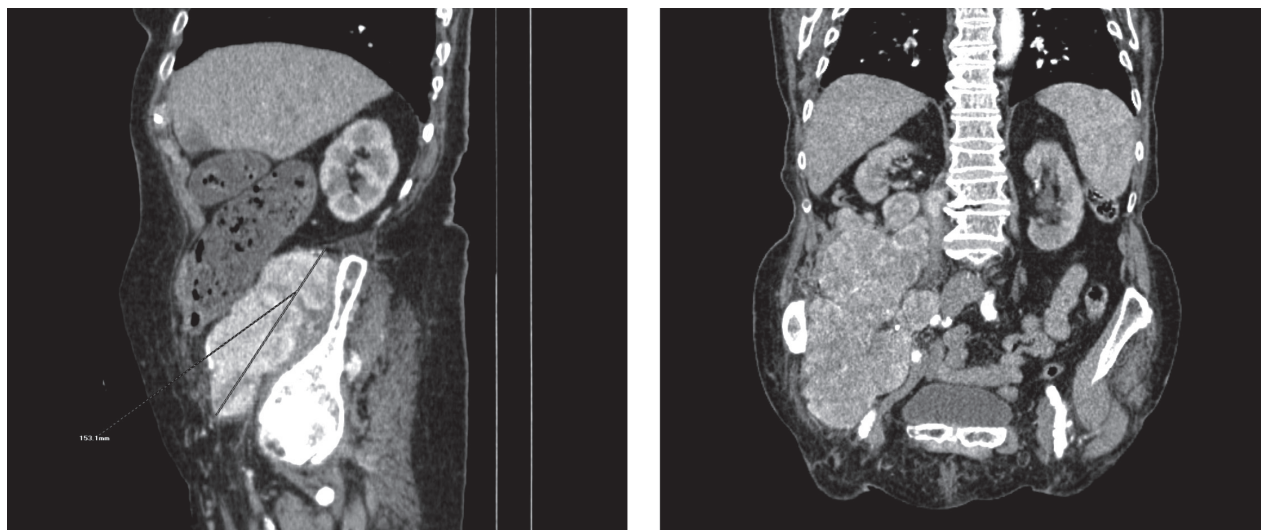


Figure 1. The Computed tomography images shows the big Haemangiopericytoma

plasma proteins and causing an increase of the free fraction of IGF-II inducing hypoglycemia. A measurement of IGF-2 was not performed because this method is not available in our laboratory. However, the hypothesis of a paraneoplastic hypoglycemia induced by non-islet tumor appears the most plausible for the following reason: 1. we have excluded other causes of hypoglycemia; 2. IGF- is suppressed (< 100 ng/mL) so that independently to IGF2 concentration IGF2:IGF1 ratio appears high; 3. Insulin levels are low; 4 the presence of voluminous hemangiopericytoma that may be associated with this serious metabolic complication. The diagnosis is generally of exclusion because the symptoms are non-specific for this type of hypoglycemia (mental confusion, sweating, facial pallor, asthenia). The physical examination and anamnesis are essential in diagnostic workup, especially in the case of hypoglycemia without an apparent cause in which is appropriate to investigate for the presence of current or previous malignancies that can cause hypoglycemia.

To formulate the correct diagnosis is fundamental to consider insulin and c-peptide serum level in correspondence to hypoglycemia. Is also necessary to consider kidney and liver function and the possible use of oral hypoglycemic drugs. If the C-peptide and insulin concentration are low during hypoglycemia crisis you are authorized to dose IGF1, GH and IGF2 in suspected of paraneoplastic hypoglycemia. The typical

pattern of NICTH includes low serum glucose level (< 55 mg/dl), low insulin and C-peptide serum concentration and low IGF1 serum concentration. GH level are generally normal or low during hypoglycemia and IGF2 concentration may be normal depending on the specific IGF2 assay used(3-7). When IGF2 is normal the IGF1 concentration are very low (< 100 ng/mL)(8) so that the IGF2:IGF1 ratio is elevated (9) more than the normal ratio of 3:1 (10) and can achieve 10:1 (8).

Treatment

The therapy consists of three steps: in the acute phase is essential to correct hypoglycemia using parenteral solutions to high concentration of glucose; in the second phase is need remove, if possible, the tumor; if not possible remove the neoplasm, is necessary to prevent new hypoglycemic crisis through glucocorticoids drugs (eg prednisolone 40 mg/day), diazoxide or glucagon. Somatostatin analogs are not recommended.

Outcome and follow-up

With the continuous parenteral nutrition we have good controlled the patient's glucose serum concentration. However, patient's general condition has

worsened during the hospitalization and the patient developing a progressive kidney failure due to the big neoplasm compression. After some days the patient died.

Discussion

This case is a special feature in the panorama of hypoglycemia because only a few tumors can produce this complication. Although we do not have the determination of IGF2 can believe that hypoglycemia has been supported by high levels of big IGF2 peptide since we found that both insulin and IGF 1 were greatly reduced so that IGF2:IGF1 ratio is high independently to the value of IGF2. Indeed the typical pattern of NICTH includes low serum glucose level (<55 mg/dl), low insulin and C-peptide serum concentration and low IGF1 serum concentration. GH level are generally normal or low during hypoglycemia and IGF2 concentration may be normal depending on the specific IGF2 assay used (3-7). When IGF2 is normal the IGF1 concentration are very low (<100 ng/mL)(8) so that the IGF2:IGF1 ratio is elevated (9) more than normal ratio of 3:1 (10) and can achieve 10:1 (8). Finally this case report emphasizes that an accurate anamnesis could be the key to solving a difficult clinical problem.

Patient consent

The patient is dead.

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