A clinical update on tumor-induced hypoglycemia

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Abstract

Tumor-induced hypoglycemia is a rare clinical entity that may occur in patients with diverse kinds of tumor lineages and that may be caused by different mechanisms. These pathogenic mechanisms include the eutopic insulin secretion by a pancreatic islet beta-cell tumor, and also the ectopic tumor insulin secretion by non-islet-cell tumor, such as bronchial carcinoids and gastrointestinal stromal tumors. Insulinoma is, by far, the most common tumor associated to clinical and biochemical hypoglycemia. Insulinomas are usually single, small, sporadic and intrapancreatic benign tumors. Only 5-10% of insulinomas are malignant. Insulinoma may be associated to the multiple endocrine neoplasia type 1 in 4-6% of patients. Medical therapy with diazoxide or somatostatin analogs has been used to control hypoglycemic symptoms in patients with insulinoma, but only surgical excision by enucleation or partial pancreatectomy is curative. Other mechanisms that may, more uncommonly, account for tumor-associated hypoglycemia without excess insulin secretion are the tumor secretion of peptides capable of causing glucose consumption by different mechanisms. These are the cases of tumor producing IGF-2 precursors, IGF-1, somatostatin and GLP-1. Tumor autoimmune hypoglycemia is due to the production by tumor cells of insulin or insulin receptor autoantibodies. Lastly, massive tumor burden with glucose consumption, massive tumor liver infiltration and pituitary or adrenal glands destruction by tumor are other mechanisms for tumor-induced hypoglycemia in cases of large and aggressive neoplasias.
Introduction

Hypoglycemia not associated with diabetes and/or its therapy is an uncommon clinical disorder. In people without diabetes the diagnosis of hypoglycemia is usually established when venous plasma glucose is <55 mg/dl (3 mmol/l) and supported by the presence of Whipple’s triad (symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after raising plasma glucose concentration) (1).

In ill or medicated adults without diabetes, the most common causes of hypoglycemia are drugs other than insulin or insulin secretagogues. Other etiologies are critical illnesses and hormone deficiencies (cortisol and glucagon). In seemingly well non-diabetic individuals hypoglycemia is usually associated with endogenous hyperinsulinism due to nesidioblastosis, tumor beta-cell disorders, and insulin autoimmune hypoglycemia. On other occasions the etiology of hypoglycemia in these patients can be accidental, surreptitious or malicious (1). Lastly, tumor hypersecretion of several factors with hypoglycemic effects have been also documented.

Tumor-induced hypoglycemia (TIH) is a rare clinical type of hypoglycemia that usually appears as a result of insulin hypersecretion by a pancreatic islet beta-cell tumor (insulinoma). However, TIH can also be developed by other non-pancreatic tumors (non-islet-cell tumor hypoglycemia, NICTH). This review focuses on the most updated and relevant clinical, diagnostic and therapeutic aspects related to TIH, as well as different clinical situations related to insulinoma, the most common cause of TIH.

Pathophysiology of tumor-induced hypoglycemia

Several pathogenetic mechanisms may explain TIH (table 1 and figure 1). The most common cause, although rare, is tumor hyperinsulinism induced by a pancreatic islet beta-cell tumor (insulinoma). However, NICTH is nowadays a well recognized etiology of TIH (2). In this case the main etiology of hypoglycemia is the release by the tumor of insulin-like growth factor 2 (IGF-2) or its high-molecular-weight precursor (big IGF-2) (3-11). Other mechanisms for NICTH are IGF-1 tumor secretion (12), the production of autoantibodies to insulin (13) or its receptor (14), or more rarely, the secretion of glucagon-like peptide-1 (GLP-1) (15, 16), and massive tumor burden (17). Lastly, ectopic insulin secretion by a non-islet-cell tumor has also been exceptionally reported (18-23).

Insulin-secreting tumors

Eutopic tumor insulin secretion: pancreatic islet beta-cell tumor (insulinoma)

Insulinoma is a rare tumor with an incidence of 0.4 per 100,000 person-years (4 cases per million per year), more frequently observed in the fifth decade of life (median age 47 yr; range 8 to 82 yr) and with a slight predominance (~60%) for the female sex (24). This tumor is
the most common (~25%) functioning pancreatic neuroendocrine tumor (pNET). Insulinomas are usually single, small (usually <2 cm diameter), well-circumscribed, benign, sporadic, intrapancreatic tumors and evenly distributed throughout the pancreas (figure 2) (24-27).

Hypoglycemic symptoms secondary to excessive and uncontrolled secretion of insulin by the tumor usually occur in the fasting state (73%); however, they can also be present only in the postprandial state (6%) and in both fasting and postprandial states (21%) (28). Correct diagnosis is often delayed until 2 years from the onset of symptoms due to the fact that, on many occasions, neuropsychiatric or neurologic symptoms are misunderstood (1, 24, 29). Hypoglycemic symptoms can be neurogenic (autonomic) (hunger, sweating, paresthesia, palpitations, diaphoresis, anxiety and tremor) and neuroglycopenic symptoms (confusion, visual disturbances, behavioural changes, epileptic seizures, confusion, and coma) (30). Weight gain and obesity as a consequence of frequent small meals to avoid hypoglycemic symptoms is a well known clinical sign of insulinoma (31, 32).

Biochemical diagnosis of insulinoma is established when hypoglycemia, supported by the presence of Whipple's triad, is associated with endogenous hyperinsulinism showing the following criteria: fasting plasma glucose concentrations are <55 mg/dl (3.0 mmol/l), plasma insulin concentrations ≥ 3 µU/ml (18 pmol/l), plasma C-peptide concentrations ≥ 0.6 ng/ml (0.2 nmol/l), plasma proinsulin concentrations ≥ 5 pmol/l, plasma beta-hydroxybutyrate levels ≤ 2.7 mmol/l, change in blood glucose ≥ 25 mg/dl (1.4 mmol/l) at 30 min after 1 mg intravenous glucagon, a negative sulphonylurea screen in the plasma and/or urine and no circulating antibodies to insulin (1). When Whipple’s triad has not been documented in a patient with suggestive clinical evidence of hypoglycemia or when biochemical study during the hypoglycemia could not be performed, the patient should undergo a supervised 72-hour fast test with the aim to reproduce the hypoglycemic episode. Diagnosis of insulinoma must be confirmed by localizing the tumor by imaging conventional studies, such as computed tomography (CT), magnetic resonance imaging (MRI) and transabdominal ultrasonography. These localizing techniques detect most insulinomas (figure 2); however, due to the small size of some tumors, a negative study does not always exclude its presence (1, 33, 34).

Although medical therapy with frequent carbohydrate meals and diazoxide (~200-600 m/day orally) or somatostatin analogs may control hypoglycemic symptoms in 50-60% of patients, only surgery is curative (26, 29). Therefore, once the tumor has been located, the treatment of choice is surgical excision. The surgical method usually employed (~60%) is enucleation of the tumor, followed by partial pancreatectomy (24). Although the majority of the interventions have been made using open surgery, laparoscopic surgery is a surgical option in some centers with a morbidity rate comparable to that for the open approach. When the tumor is not found during laparoscopy, laparoscopic ultrasonography seems to be the most efficient tool to localize it and probably to prevent conversion (35, 36). Those tumors located in the body
or tail of the pancreas can better benefit of laparoscopic approach (37). Alternative medical treatment may be necessary for symptomatic patients with unresectable or for those who are not candidates for surgical treatment or refuse surgery (1, 33, 34). It has been recently reported the alternative option of the use of endoscopic ultrasonography (EUS) or intraoperative (IO) US-guided ethanol fine-needle injection for the treatment of symptomatic insulinomas requiring extensive resection and for poor surgical candidates (38).

Highlights of different special clinical situations related with insulinoma are presented below.

**Occult insulinoma**

A small number of insulinomas remain occult after conventional (ultrasonography, CT scan and MRI) localizing preoperative study (26). In some cases, pancreatic dynamic consecutive enhanced CT scanning may help to localize the tumor (39). Somatostatin receptor scintigraphy detects between 20% and 50% of affected patients with benign insulinomas (34, 40). The abundance of glucagon-like peptide type 1 receptors (GLP-1R) in pancreatic β-cells in insulinomas has led to the development of GLP-1-receptor scanning by using GLP-1-like radioligands with high binding affinity to GLP-1 receptors to localize occult insulinomas (41). GLP-1R scan with $^{111}$In-DOTA-exendin-4 successfully detected two occult insulinomas not identified by conventional localizing study (42).

Selective arterial calcium stimulation (SACS) with hepatic venous sampling for insulin quantification, with an endpoint of a greater than 2-fold increase in hepatic venous insulin levels over baseline, has shown a high sensitivity (93%) for localization of insulinoma (28). The combination of SACS with EUS achieved tumor localization in all patients diagnosed in the period 1998-2007 at the Mayo Clinic avoiding blind pancreatic exploration (28). Occult insulinomas are usually located within the pancreatic head (43, 44). Given the associated morbidity and lack of surgical success, blind distal pancreatectomy and progressive pancreatectomy are not recommended in cases of occult insulinoma at the present time (26, 44). Palpation and IOUS permit detection of virtually all insulinomas, including reoperated cases (26, 44, 45). Lastly, the use of gamma-probe intraoperatively after $^{111}$In-DOTA-exendin-4 administration permitted the detection and successful surgical removal of all insulinomas in a series of six patients, one of them with ectopic insulinoma (42).

**Extrapancreatic (ectopic) insulinoma**

Ectopic insulinoma is an extremely rare (~2%) entity whose diagnosis should be suspected when a biochemically confirmed insulinoma is not localized (26). These tumors are usually located in the duodenal wall; although other locations such as duodenohepatic ligament and surrounding tissues of pancreas have been reported (46, 47). Ectopic insulinomas usually develop on ectopic (heterotopic, accessory, or aberrant) pancreas, an entity reported in
0.5-15% of autopsies and in 1 out of 500 abdominal surgeries, mainly found in the stomach, duodenum and jejunum (46-48).

Insulinoma associated to multiple endocrine neoplasia type 1

Insulinoma is the second most common (10-30%) functioning pancreatic tumor associated with multiple endocrine neoplasia (MEN) type 1, after gastrinoma. On the contrary, only 4-6% of patients with insulinoma will develop MEN 1 (1, 28, 49). Unlike sporadic insulinomas that usually develop after the age of 40 years, MEN-associated insulinomas occur usually at age under 40 and even under 20 years (24, 50). This explains why in 10% of MEN 1 patients insulinoma will be the first tumor to appear. On many occasions tumors are multiple at the time of diagnosis and up to 10% they can be associated with other pNETs (49). Metastases are present in up to 50% of patients with MEN 1-associated insulinomas, compared with less than 10% of non-MEN 1 insulinomas (51). In the absence of distant metastases, surgery is advocated for MEN 1 insulinomas. Surgical therapy ranges from enucleation in isolated tumors to distal subtotal (80-85%) pancreatectomy combined with enucleation of tumors in the pancreatic head in those cases with multiple tumors (49, 51). Surgery is usually performed in MEN1-associated insulinoma even if the tumor cannot be identified by imaging due to the intense symptoms caused by hyperinsulinemia. Lastly, because insulinomas in these patients are usually multicentric, complete surgical resection is more difficult and local tumor resection often results in disease recurrence (52, 53).

Recurrent insulinoma

Insulinoma-induced hypoglycemia can recur after successful surgical removal (54). It can develop from 4 to 20 yr after initial surgery. Recurrence rate for insulinoma after initial pancreatic exploration was 5% and 7% at 10 yr and 20 yr, respectively, in patients with sporadic insulinoma and 21% at 10-20 yr in patients with MEN 1, in a 60-year observation period study (from 1927 through 1986) performed in 224 Mayo Clinic patients (24). Recurrence of hyperinsulinemic hypoglycemia after a brief interval (<4 years) during which hypoglycemia (both symptomatic and biochemical) is absent suggests regrowth of remnant insulinoma (54).

Malignant insulinoma

Approximately 5-10% of insulinomas are malignant with distant metastasis at diagnosis (figure 2), mainly to the liver and regional lymph nodes, with a reported 10-year survival rate of less than 20% (55). On many occasions they are indolent tumors associated to prolonged survival. The patient can undergo pancreas and liver resection (if possible) during the same operation. Lymph node dissection should be also performed if there was evidence of nodal disease. Resection of liver metastases must be considered especially when metastatic disease is confined to the liver and surgery can remove >90% of tumor (27, 56). This surgery may provide effective palliation and probably prolonged survival. Other approaches for the treatment of liver disease include hepatic artery embolization, radiofrequency ablation and crioablation.
As opposed to benign insulinomas, malignant insulinomas often express somatostatin receptor subtype 2, showing positive somatostatin receptor scintigraphy in 73% of cases (57), which can be targeted therapeutically with long-acting somatostatin analogs and peptide radionuclide receptor therapy (radioembolization) (58, 59).

Malignant insulinomas generally respond poorly to traditional chemotherapeutic agent regimens (fluorouracil, doxorubicin, and streptozocin) (60). Rapamycin (sirolimus) and everolimus, a rapamycin analog, are mammalian target of rapamycin receptor (mTOR) antagonists that may provide a useful tool for stabilizing tumor growth and controlling hypoglycemia in malignant insulinomas by reducing the malignant β-cell growth and proliferation as well as inhibiting insulin production (60-62). In fact, the addition of everolimus resulted in abolition of hypoglycemia and stabilization of disease on imaging over 45 months in a patient with unresectable metastatic insulinoma and intractable hypoglycemia (62). In selected patients with unresectable liver metastases of malignant insulinoma, liver transplantation (LT) is a therapeutic option (63). Although this technique has achieved prolonged survivals, up to 5 years, in some reported patients (64), the limited clinical experience due to the small sample size (4% of all cases of LT for metastatic NETs) (63)) makes this therapeutic procedure be currently considered as an investigational approach for patients with liver metastatic insulinoma.

Ectopic tumor insulin secretion: non-islet-cell tumors

A small number of non-islet-cell tumors have been associated with ectopic insulin secretion so far (table 1) (18-23). Among them are bronchial carcinoid tumor (18), squamous-cell carcinoma of the cervix (19), neurofibrosarcoma (65), schwannoma (20), paraganglioma (21, 23), small-cell carcinoma of the cervix (22), and gastrointestinal stromal tumor (66). Although in some of these cases there were alternative mechanisms for hypoglycemia and the possibility of pancreatic insulinoma was not definitely excluded, other more recent clinical reports (22, 23) have clearly shown that non-islet-cell tumors was the origin of the hyperinsulinemia on the basis of the detection of proinsulin mRNA and insulin protein within the tumor cells.

Mechanisms other than excess insulin

Tumor IGF-2 precursors secretion (big IGF-2) “IGF-2-oma”

NICTH due to IGF-2 was initially reported by Daughaday et al in 1988 in a 67-year-old woman who presented with recurrent severe hypoglycemia and a large thoracic leiomyosarcoma which resolved after tumor resection (67). The tumor showed high concentrations of IGF-2 mRNA and IGF-2 immunoreactive in form of a large precursor molecule, and a similar fraction of high-molecular-weight IGF-2 in the serum of the patient. Since the first report there have been many clinical cases of NICTH secondary to IGF-2 tumor hypersecretion by other type of tumors (3-11, 68) (table 1). This pathogenic mechanism is the
main cause of NICTH (2, 69) and it has been proposed the term “IGF-2-oma” to describe these
type tumors (70).

The main mechanism in IGF-2-induced NICTH is the overexpression of the IGF-2 gene
(structurally homologous to the insulin gene) by the tumor which is associated by the tumor
secretion of incompletely processed precursors of IGF-2 (pro-IGF-2 or big IGF-2) with a
persistent insulin-like activity (2, 69, 71, 72). Pro-IGF-2 is expressed in a broad spectrum of
malignant and benign tumors and binds poorly to its binding proteins, thus increasing the
likelihood that the molecule freely penetrates tissue spaces. Big IGF-2 suppresses both GH and
insulin at pituitary and pancreas levels, respectively. Due to the suppression of GH secretion,
synthesis and secretion of IGF-1 and IGF binding-protein 3 (IGFBP-3) are also decreased.
Although serum level of total IGF-2 may be normal, both the ratios pro-IGF-2 to IGF-2 and IGF-
2 to IGF-1 may be elevated (2, 69, 73). In one study the IGF-2/IGF-1 ratio ranged from 16.4 to
64.2 with a mean of 35.0 ± 2.2 in a group of patients with NICTH with big IGF-2 (69). Lastly,
basal immunoreactive insulin levels are low in these patients (69, 74) (table 2). The elevated
bioavailability of both big and free IGF-2 increases peripheral glucose consumption and
decrease glucose liver production giving rise to the development of hypoglycemia (1, 2, 69).

In a retrospective study performed in 78 patients (44 males, 56%; age at diagnosis 62 ±
1.8 yr, range; 9-86 yr) with NICTH and high serum levels of big IGF-2, Fukuda et al., 2006 (69)
found that hypoglycemic attack (confusion, incoordination, difficulty in waking in the morning
and sweating and coma) was the onset of disease in 48%, but the tumor was revealed prior to
the occurrence of hypoglycemia in 52%. Hepatocellular carcinoma and gastric carcinoma were
the most common causes of NICTH and the diameters of the tumors were more than 10 cm in
70% of the patients. All these data suggest that hypoinsulinemic hypoglycemia associated with
the presence of a large tumor supports the diagnosis of IGF-2 producing NICTH (69).

Treatment should be aimed at immediate correction of hypoglycemia, followed by
treatment directed at the underlying tumor and, finally, prevention of recurrent hypoglycemia if
the tumor cannot be cured. In these cases, long-term management with glucocorticoid therapy
has been demonstrated to consistently reverse the biochemical abnormalities caused by tumor-
derived big IGF-2 and it has been suggested that this therapy alone or in combination with
human growth hormone with or without the addition of long-acting glucagon, as the most
effective therapy in alleviating intractable hypoglycemia (75).

Tumor somatostatin secretion “Somatostatinoma”

Somatostatin-producing tumors or somatostatinomas are rare NETs (~1% of
gastroenteropancreatic-NETs) derived from D cells with an annual incidence of 1 in 40 million
(76). Since first description by Larsson et al., in 1977 (77) about 200 cases have been reported.
Somatostatinomas usually arise in the pancreas and duodenum (~90%) with approximately
equal frequency (78, 79). Extrapancreatic somatostatinomas (carcinoid somatostatinomas) can
arise in other locations as jejunum (80) and ovary (81). The most common symptoms are abdominal pain and weight loss and, in some occasions (~10%) they produce somatostatinoma syndrome (diabetes mellitus, cholelithiasis and diarrhea with steatorrhea) due to excessive secretion of somatostatin, a hormone that inhibits gastrointestinal motility and secretion as well as the release of many hormones including insulin and glucagon. Somatostatinoma-induced hypoglycemia is uncommon with isolated cases reported to date (81-84). In 3 out of 4 reported cases the tumor was located in the pancreas (82-84) and only one in the ovary (81). The mechanism of somatostatinoma-induced hypoglycemia is not clear. It seems to be related to the suppression of glucagon, GH, and other counterregulatory hormones by somatostatin. Due to somatostatin-producing endocrine tumors are frequently malignant (~70) surgical resection is the first-line therapy for localized tumors (85). Hypoglycaemia is rarely sensitive to the hyperglycemic effects of diazoxide (82). Blood glucose level is usually stabilized after surgery (81, 84) or chemotherapy (82).

Tumor IGF-1 secretion “IGF-1-oma”

NICTH due to overproduction and secretion of IGF-1 (IGF-1-oma) is an exceptional event. In fact, to our knowledge, only one patient has been reported so far (12). She was a 64-yr-old woman admitted due to severe recurrent non-hyperinsulinemic hypoglycemia. No signs of acromegaly were present. The patient was diagnosed of pulmonary large cell carcinoma with axillary metastasis. Serum total and free IGF-1 concentration was elevated, whereas GH, IGFBP-3, acid-labile subunit (ALS) and big IGF-2 were normal, and serum insulin and C-peptide were suppressed. Immunohistochemistry demonstrated IGF-1 peptide in some tumor cells and IGF-1 mRNA was detected by in situ hybridization in virtually all tumor cells. Hypoglycemic episodes did not recur after chemotherapy. The mechanism of hypoglycaemia proposed by the authors would be related with an increase in the amount of free IGF-1 which would reach insulin target tissues exerting insulin-like effects. The absence of acromegalic features might be explained by the absence of a sustained combined elevation of GH and IGF-1 and the relatively short duration of paraneoplastic hormonal changes (12).

Tumor GLP-1 secretion “GLP-1-oma”

GLP-1 is a gut peptide that stimulates both insulin release from pancreatic beta-cells and beta-cell hyperplasia. Paraneoplastic GLP-1 hypersecretion causing reactive hypoglycaemia was initially reported in 2003 in a patient with an ovarian NET (15). She was a 45-year-old woman with type 2 diabetes who developed episodes of symptomatic postprandial hypoglycaemia which cured with tumor surgery. Nine years later, in 2012, a second clinical case was reported (16). He was a 56-yr-old male with a previous diagnosis of diabetes who presented with fasting hypoglycaemia. Clinical study demonstrated a glucagon-secreting pNET, which was the likely cause of diabetes, whereas hypoglycaemia was caused by insulin secretion from hyperplastic β-cells stimulated by metastases-derived GLP-1. However, severe hypoglycaemia is not always associated to GLP-1 tumor secretion. In fact, two other patients
with GLP-1- and GLP-2-producing NETs and absence of symptomatic hypoglycaemia have been previously reported (86, 87).

Autoantibodies to insulin or its receptor "Tumor autoimmune hypoglycemia"

The syndrome of autoimmune hypoglycemia is an uncommon cause of hypoglycemia characterized by elevated levels of insulin in the presence of either anti-insulin antibodies (insulin autoimmune syndrome, Hirata disease) or anti-insulin receptor antibodies (type B insulin resistance) (88-90). Autoimmune hypoglycemia has also been related to tumor hypoglycemia (13, 90, 91). In this case anti-insulin antibodies or anti-insulin receptor antibodies are produced by the tumor (13). Both conditions are usually associated with inappropriately elevated insulin and they can lead to fasting hypoglycemia, postprandial hypoglycemia or both (90). Several tumors have been associated with autoimmune hypoglycemia, among them are multiple myeloma (13, 92), chronic myelomonocytic leukemia (90) and Hodgkin's disease (91).

Other tumor-related factors

Tumor hypoglycemia may be due exclusively to increased glucose consumption by the tumor mass and/or its metastases, as well as in those with massive liver tumor infiltration (93-97). Among these tumors are hepatocellular carcinoma (95, 96), meningioma (93, 94), non-Hodgkin's lymphoma (98, 99) and pheochromocytoma (97). Excessive tumor glucose consumption can become manifest through functional tests as $^{18}$F-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ($^{18}$F-FDG-PET/CT) showing remarkable glucose uptake in the tumor with reduced physiologic uptake in other organs (97). On other occasions the tumor can infiltrate and destroy different organs, such as the pituitary or adrenal glands resulting in hypopituitarism or primary adrenal insufficiency, respectively, given rise to the development of secondary hypoglycemia (100).

Conclusion

Tumors are a rare cause of hypoglycemia. TIH is usually due to the tumor hypersecretion of insulin by pancreatic beta cells derived tumors (insulinomas). However, there are other tumors that have the capability of producing hypoglycemia by mechanisms other than the endogenous hyperinsulinism. It should be kept in mind this diagnostic possibility since hypoglycemia in this case can manifest as a paraneoplastic symptoms of a tumor with a potentially serious prognosis.

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Legend for the figures

Figure 1. Diagnostic algorithm for patients with suspected tumor hypoglycemia.

Figure 2. Abdomen CT scan image with intravenous contrast in a woman with a 1.5 cm benign insulinoma (white arrow) located in the head of the pancreas (A). Abdomen CT scan with contrast showing three small images (black arrow) compatible con multiple insulinomas in the head of the pancreas in a female patient (B). CT scan without contrast of the abdomen showing multiple liver metastases in a female patient with malignant insulinoma (C).
Suspected tumor-induced hypoglycemia

Hyperinsulinemia

Yes

Localizing study

Eutopic tumor insulin secretion

- Pancreatic islet beta-cell tumor (insulinoma)
- NICTH
- Ectopic insulinoma

Ectopic tumor insulin secretion

Mechanisms other than excess tumor insulin secretion

No

Autoantibodies to insulin or its receptor

Positive

Hematological malignancy*

Negative

Occult insulinoma vs nesidioblastosis

NICTH

IGF-2-oma

Somatostatinoma

IGF-1-oma (?)

GLP-1-oma

*After excluding other non tumor causes of autoimmune hypoglycemia

NICTH: non-islet-cell tumor hypoglycemia