Clinical characteristics and management of insulin-producing neuroendocrine carcinomas

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Abstract

Background and study aims: **Due to rarity of insulin-producing pancreatic neuroendocrine carcinomas, no large, nor randomized studies of the clinical course, treatment options and outcome are available. Therefore, we want to share our personal experience and we retrospectively reviewed a cohort of five patients.**

Patients and methods: **This study reports on the clinical characteristics, disease course, management and outcome of five patients with an advanced pancreatic neuroendocrine carcinoma with insulin production, which we followed recently in our center (between 2006 and 2015). Extraordinary for our cohort is that, except for one patient, which was diagnosed with a de novo malignant insulinoma, all other patients were diagnosed with a non-functional pancreatic neuroendocrine tumor which evolved during the disease course to a malignant insulinoma.**

Results: **Although various treatment strategies, both surgical and medical, are used to prolong survival and prevent hypoglycemic events, long-term prognosis of these patients remains poor, especially after transformation of a non-functional pancreatic neuroendocrine tumor to an insulin-producing neuroendocrine carcinoma. Of all five patients, only one is still alive, the other four died 25, 17, 3 and 1 month(s) after diagnosis of the malignant insulinoma. In general, prognosis is determined by early diagnosis and treatment, and by resectability of the tumor and its biological behavior.**

Conclusions: **Management of a malignant insulinoma is very challenging and a better understanding of the underlying mechanisms of this disease entity and its biological behavior is absolutely necessary to improve diagnostic tools, treatment and outcome in the future.** (Acta gastroenterol. belg., **2016**, 79, **321-327**).

Key words : insulinoma, pancreatic neuroendocrine tumor, refractory hypoglycemia, treatment

Introduction

Classically, insulinomas are rare, insulin-secreting and well-differentiated neuroendocrine tumors of the pancreas (incidence 4:1000 000 every year) and comprise 1 to 2% of all pancreatic neoplasms (1,2,3). The majority of insulinomas occur sporadically, though 5 to 10% are related with type 1 multiple endocrine neoplasia (1,3). In 90% of the cases, insulinomas are benign, solitary, small (< 2 cm) with an intrapancreatic localization (1,2,3,4). Only 5 to 10% of these insulinomas are advanced and poorly differentiated insulin-secreting neuroendocrine carcinomas, appointed as malignant insulinomas.

The diagnosis of an insulinoma is established by confirming hypoglycemia due to uncontrolled or inadequately suppressed insulin production (5) in combination with neuroglycopenic symptoms which promptly disappear after administration of glucose (Whipple's triad) (2,3).

The distinction between a benign or malignant insulinoma can only be made by the presence of metastases, mostly in the lymph nodes or in the liver, and not only based on clinical presentation, biochemistry, histological features or genetics (1,6).

Because of the nonspecific symptoms of hypoglycemia or this disease, diagnosis is often late (2). However, early recognition is of major importance because of the risk of a life-threatening hypoglycemia.

Due to its rarity, multiple questions concerning etiology, pathogenesis and best treatment strategy remain unanswered and a solid consensus is absent. Therefore, we want to share our personal experience and report here on the clinical course, treatment and outcome of five patients we followed recently with an advanced neuroendocrine carcinoma with insulin production.

Patients and methods

All five patients were in follow-up in the University Hospitals of Leuven from November 2006 till April 2015. The data were extracted from the patient files. For each of these five patients, the presence of a malignant insulinoma was confirmed by radiological imaging and histological examination. Patient characteristics are presented in Table 1.

Results

Patient 1

In March 2013, a 24-year-old woman was diagnosed with a high-grade pancreatic neuroendocrine tumor (pNET) type malignant insulinoma (Ki-67 index of 28%) with retroperitoneal lymph nodes and multifocal liver metastases. Diagnosis was made after several

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Table 1. — **Overview of patient characteristics**

	malignant insulinoma				
	de novo	originated from a pancreatic neuroendocrine tumor			
	patient 1	patient 2	patient 3	patient 4	patient 5
Sex	female	male	female	male	female
Age	24	53	31	53	57
Time interval between diagnosis of pNET and transformation to a malignant insulinoma in years (y) and months (m)	not applicable	2y 5m	1y 11m	3y 1m	6y 5m
Biochemistry - Reference value					
Chromogranin (40-170 μg/L)	6990	92000	2840	2750	4590
Glucose (60-105 mg/dl)	<20	49	37	39	43
Insulin (2,6-24,9 mU/L)	88	85	22,4	141	30
C-peptide (0,20 - 0,80 nmol/L)	2,4	3,8	0,9	5,6	1,8
72h fasting test	+	not performed	+	not performed	+
Histological examination					
Biopsy	liver metastasis	liver metastasis	lymph node	liver metastasis	liver metastasis
Ki67 (%)	28	21	20	40	2-20
Chromogranin	+	+	+	+	+
Synaptophysin	+	+	+	+	+
Insulin	-	+	+	not performed	+
Treatment					
Surgery	-	-	-	-	+
Medical treatment* (ordered chronologically during the disease course)					
Diazoxide	2	4	5	6	2
Somatostatin analogues	2	4	2 5	1 6	2 4
Everolimus	1 2 3	3 4	5	2	1 2 4
Sunitinib		2	3	3	
Chemotherapy	4	1 5	1 2	4	
PRRT	3		4	5	
TACE	5	6	6		3 4
Outcome	died	died	died	died	alive
After diagnosis pNET	2y 1m	2y 9m	2y 2m	3y 2m	-
After transformation to a malignant insulinoma	2y 1m	1y 5m	3m	1m	-

Pancreatic neuroendocrine tumor (pNET), peptide receptor radionuclide therapy (PRRT), transarterial chemoembolization (TACE).

* In the section treatment of this table, the numbers refer to the sequence of therapy (with number 1 indicating the first treatment, number 2 the second treatment, number 3 the third treatment…).

episodes of symptomatic hypoglycemia including bizarre and aggressive behavior, decreased consciousness, intermittent tremor and weight gain (> 5 kg during the last month due to the need for extra meals at night). The medical or familial history was unremarkable. Laboratory, radiological and histological results at initial presentation are displayed in Table 1.

To correct hypoglycemia, treatment with hypertonic glucose and everolimus (10 mg/day) was started. Because of a suboptimal effect, diazoxide (2x 100mg/day) - in combination with acetazolamide for progressive edemas - was associated. Given the side effects (nausea, vomitus), a dose reduction of diazoxide (2x 50 mg/d day) was necessary with eventually even complete withdrawal. After combining octreotide (3x 0.5 mg/day) and subsequently change to the long-acting release form (LAR) 30mg/month in combination with everolimus 10mg/day, a good glycemic and tumor control was

obtained. However, in January 2014, a CT scan showed disease progression with increasing volume of the pancreatic tumor, lymph nodes and liver metastasis in absence of symptoms. Given an intense expression of somatatostatin receptors in the pancreatic tumor and all metastases on Ga-68 Dotatate PET-CT scan, treatment with everolimus 5 mg/day was combined with peptide receptor radionuclide therapy (PRRT). After four cycles of ^{177}Lu octreotate at 8-wk intervals (up to a total administered activity of 29.6 Bq), multifocal bone metastases developed. In February 2015, disease progression continued with recurrent hypoglycemia, diarrhea, flushing, elevated chromogranin, increasing liver and bone metastases and new lung metastases. Given this evolution, everolimus was stopped and chemotherapy (cisplatin 80mg/m^2 on day 1 and etoposide 100mg/m^2 on day 1,2,3 q3w) was started.

Unfortunately, after administration of two cycles chemotherapy, again, a hypoglycemic coma due to insulin overproduction occurred. Despite high dose corticosteroids, hypertonic glucose of 50% and octreotide, an adequate control of glycemia could not be obtained. Rescue therapy with intrahepatic administration of doxorubicin beads (50 mg/m^2) was not successfull either: a tumor lysis syndrome with acute liver failure, encefalopathy and renal insufficiency occurred. This patient died in April 2015.

Patient 2

In August 2011, a 53-year-old man presented with weight loss and abdominal discomfort: a CT scan showed a pancreatic tumor with liver metastases. Histology of a liver metastasis revealed a high-grade NET (Ki-67 index of 21%). Except for coronary artery disease, this patient had no medical or familial history. Laboratory, radiological and histological results at initial presentation are displayed in Table 1.

Given the poor differentiation grade of this tumor, chemotherapy (cisplatin 80 mg/m^2 day 1, etoposide 100mg/m^2 day 1,2,3 q3w) was started. Because of disease progression after administration of 4 cycles, chemotherapy needed to be discontinued and in November 2011 sunitinib was started (37.5mg/day). In March 2012, two bone metastases were suspected, but treatment with sunitinib was continued because of stable disease at other sites, good clinical evolution and excellent drug tolerance. In November 2012, recurrent early morning hypoglycemia occurred together with a rise of chromogranin, although a CT scan showed a stable disease according to the RECIST criteria. Sunitinib was changed to everolimus (10mg/day) whereby maintaining a stable disease till December 2013. A new liver biopsy in one of the metastases was performed and confirmed a metastasis of a NET type insulinoma. In December 2013, again consecutive episodes of symptomatic hypoglycemia with coma occurred and a CT scan confirmed major disease progression at the liver. Despite hypertonic glucose, octreotide (0.5mg 3x/day and secondly LAR 30mg/month) and diazoxide (3x 100mg/day) in combination with everolimus 10mg/day, glycemic control was extremely difficult: for this reason, chemotherapy type modified Folfox (oxaliplatin 85mg/m^2 day 1, levofolic acid 200mg/m^2 day 1, fluorouracil 400mg/m^2 bolus day 1-2 in combination with continuous infusion of 2400mg/m^2/46h q2w) was started. Unfortunately, a good glycemic control could not be accomplished, even not after combining corticosteroids with everolimus. Because of progressive clinical deterioration with confusion and coma due to recurrent hypoglycemia, intrahepatic administration of doxorubicin beads (50mg/m^2) was performed twice without success. Due to growth of the liver metastases and possible factor drug toxicity, liver failure developed with hepatic encephalopathy. Given the poor condition of this patient, further treatment was impossible. The patient died in April 2014.

Patient 3

In June 2009, diagnosis of a high-grade NET (Ki-67 index of 20%) was made in a 31-year-old woman after punction of a palpable supraclavicular lymph node. Further staging revealed a primary tumor in the pancreas together with liver metastases and lymph nodes at the base of the neck, presacral and para-aortic. Initially, a wait-and-see policy was chosen because of only very slow evolving disease. After three months, chemotherapy was started (first 3 cycles carboplatin AUC5 day 1 – etoposide 100 mg/m^2 day 1, 2 and 3 q3w; second - because of disease progression under this regimen - switch to doxorubicin 50mg/m^2, cyclophosphamide 600mg/m^2 and cisplatin 50mg/m^2 day 1 q3w in combination with octreotide 20mg/month). After four cycles doxorubicin-cyclophosphamide-cisplatin with octreotide, disease progression occurred again: chemotherapy and octreotide were replaced by sunitinib 37,5 mg/day. Because of hand-foot syndrome grade III, leucopenia and thrombopenia a dose reduction to 25mg/day was mandatory. After eight months treatment with sunitinib, disease progression was reported and the patient was referred to our hospital. Because of intense expression of somatostatin receptors on Ga-68 Dotatoc PET-CT scan in the pancreatic tumor and in all metastatic lesions, PRRT was started: four cycles of ^{90}Ytrium dotatoc were administered at 8-wk intervals up to a total activity of 10.5 GBq. In May 2011 (one month after the last PRRT), a hypoglycemic coma occurred. Revision of the histological findings and an insulin staining of the initial biopsy in the supraclavicular lymph node was compatible with a metastasis of an insulinoma. In order to control glycemia, parenteral nutrition, diazoxide, octreotide and everolimus were started. Everolimus had to be discontinued because of drug induced thrombopenia. After achieving normal glycemic levels, everolimus was reintroduced at a lower

dose (5mg/day) but had to be stopped again because of progressive disease and refractory edemas. In August 2011, hypoglycemia was not present anymore, but in an attempt to achieve tumor control, intrahepatic administration of doxorubicin beads (50mg/m^2) was performed. Because of progressive clinical deterioration and a poor general condition, it was not possible to repeat this administration. The patient died at the end of August 2011.

Patient 4

In August 2008, a 53-year-old man was diagnosed with a large, high grade pNET (Ki-67 index of 40%) with retroperitoneal lymph nodes and liver metastases. After three months of treatment with octreotide (LAR 30mg/month), a CT scan showed a volume increase of the liver metastases.

Therefore, in the context of inclusion in the RADIANT-3 trial (RAD001 versus placebo with crossover if progressive disease under placebo) (7), RAD001 was started. A very good therapy response and tolerance were present, except for the development of new bone lesions at Th7 and the right eighth rib. In January 2010 – fourteen months after starting RAD001 – obvious disease progression was documented and therapy was changed into sunitinib (37.5 mg/day). CT scan showed a stable disease, but after two months sunitinib had to be discontinued because of drug intolerance (weight loss, vomiting and abdominal discomfort). Chemotherapy (cisplatin100mg/m^2 day 1, etoposide 80mg/m^2 day 1,2,3 q3w) was introduced with a good clinical and radiological response till March 2011. Despite a high proliferation index, PRRT was considered given the intense somatostatin receptor expressing character of the primary tumor and the metastases in the liver, retroperitoneal lymph nodes and bone on a Ga-68 Dotatoc PET-CT scan. Four cycles of ^{90}Ytrium dotatoc were administered at 8-wk intervals up to a total activity of 12.11 GBq. Short after the fourth and last ^{90}Ytrium dotatoc administration in September 2011, episodes of symptomatic hypoglycemia occurred: hypertonic glucose in combination with diazoxide (3x 200 mg/day) and octreotide (3x 0.5mg/day) were started, thereby achieving a good glycemic control. The patient refused any further treatment - despite possibility of intrahepatic chemotherapy – and preferred palliative care. He died in October 2011.

Patient 5

In November 2006, a 57-year-old woman, was diagnosed with an intermediate grade pNET (Ki-67 index of 2-20%) and a hypervascular mass in segment of the liver after performing a CT scan for persisting diarrhea. Surgical exploration confirmed a pancreatic tumor and a liver mass in segment 5, but with extension to segment 2 and 3 and presence of peripancreatic lymph nodes. Therefore, surgery included resection of the pancreas tail, splenectomy, segmentectomy 4b and 5 of the liver and metastasectomy at segment 2 and 3. No signs of disease recurrence were documented until November 2008: then, a rise in chromogranin and multiple liver and lung metastases became apparent. The patient was included in the RADIANT-3 trial (7): she initially received the placebo and because of disease progression she crossed over to everolimus 10mg/day in July 2009. Stable disease could be maintained till May 2013 when recurrent symptomatic hypoglycemia occurred. Revision of histological findings of 2006 and a new biopsy in one of the liver metastases were both compatible with an insulinoma. Hypertonic glucose and octreotide (first 3x 0.5mg /day, secondly LAR 30mg/month) were associated to everolimus 10mg/day. Because insufficient glycemic control, diazoxide (2x 100mg/ day) was combined, though had to be withdrawn because of deterioration of renal function, edema and refractory hypoglycemia at night. In June 2013, intrahepatic administration of doxorubicin beads (50mg/m^2) was performed. After obtaining stable glycemic levels, everolimus (10mg/day) and octreotide (30mg/month) were restarted. Under this regimen the patient did well till August 2014: at that time, progressive disease with symptomatic hypoglycemia and volume increase of liver metastases was present. For the second time, intrahepatic doxorubicin beads (50mg/m^2) were administered; everolimus 10mg/day and octreotide LAR 30mg/month were continued. Radiological imaging after two months showed a partial response with a volume decrease of the liver metastases. At this moment, the patient is doing well.

Discussion

Malignant insulinomas are a rare and very challenging disease. Given the rarity, there are no large, nor randomized studies of the different treatment options and outcome available (6,8,9) and many of the recommendations are based on expert opinion and derived from the management of other functional NETs. Etiology and molecular pathogenesis remain poorly understood (2,5). In addition, a few predictors of metastatic disease and decreased survival, such as tumor size ≥ 2cm, tumor grading and staging (Ki-67 ≥ 2%), overexpression of p53, cytokeratin 19 status and chromosomal instability (in particular loss of 3p or 6q; gain on 12q,14q or 17pq) could be identified (10).

The results of follow-up of five patients with a sporadic malignant insulinoma and our experience with the various treatment options are reported here. Extraordinary for our small cohort is that, except for one patient who had the diagnosis of a de novo malignant insulinoma, all other patients exhibit a pNET which evolved during the disease course to a malignant insulinoma and this after an interval with a range of almost 2 to almost 6.5 years. The prognosis in these patients is extremely poor. The mean age of our patients at diagnosis is 44 years, which

is in agreement to the described age specific incidence peak of 50 years in literature (4,5). Only MEN1-related insulinomas typically occur earlier in life (1,3,4).

For the malignant insulinoma, multimodal treatment — which includes both surgical and medical approaches — must be considered in order to prolong survival and prevent hypoglycemic events (1,2). If technically feasible, surgery is the treatment of first choice in an attempt to cure the patient provided that complete resection is possible - or to debulk the tumorload, resulting in a reduction of insulin hypersecretion (10,11) and subsequent hypoglycemia. Data show that 30% of the malignant insulinomas are unresectable (5), this in contrast to benign insulinomas which are typically small, unique, resectable and cured after surgical resection (3). In literature, the median disease-free survival of a malignant insulinoma after curative resection is 5 years (12) with a recurrence rate of 60% within 3 years (3,5,12). Surgical resection of liver metastases can be considered if at least 90% of the tumor can be removed (1,9,13). In only one patient of our cohort, surgery was applied for a tumor in the pancreas tail, hepatic metastases and pancreatic lymph nodes. Disease recurrence was reported after 2 years. All other patients were, given the disease dissemination, not eligible for surgery and drug treatment was indicated here.

Before surgery, high-performance radiological imaging is necessary to identify and localize the primary tumor, to detect lymph nodes or metastases and to determine the type of surgery (2,3). There is no general consensus concerning the best preoperative imaging methods and preoperative localization of the tumor fails in 10-27% of patients (3). For this reason and the fact that nearly all insulinomas can be localized successfully during the operation, some centers do not perform preoperative localization studies. In our center, preoperative imaging is always performed, mainly by EUS of the pancreas, 3-phase CT and/or MRI and/or dotatoc/dotatate-PET/CT scan.

Indications for medical treatment are the irresectable malignant insulinoma, and presence of a contraindication for surgery or refusal by the patient (2). To normalize blood glucose levels in an acute hypoglycemic event, intravenous hypertonic glucose, diazoxide (an antihypertensive benzothiadiazine), somatostatin analogs (SSA) and parenteral or enteral feedings are administered. SSA also have a negative effect on cell proliferation (1,2,14): in our personal experience, disease stabilization was achieved, but striking tumor shrinkage could not be reported, which is similar to observations in literature (9).

More intensive treatment is necessary in case of failure of the above therapies, a very aggressive and symptomatic malignant insulinoma and an extensive hepatic involvement. Beside conventional chemotherapy, experience with newer therapeutic strategies such as everolimus, sunitinib, transarterial chemoembolization (TACE) and PRRT is increasing.

Recently, the benefit of everolimus (an mTOR inhibitor) in the management of symptomatic malignant insulinoma has been suggested (14,15). Beside an antitumor effect, everolimus also induces hyperglycemia (1,14,15). Everolimus improves the median progression free survival compared with placebo (11 months versus 4.6 months) in pancreatic neuroendocrine tumors (7). Although everolimus is generally used for well differentiated NETs, all five patients of our cohort (1/5 with intermediate grade NET and 4/5 with high-grade NET) were treated with everolimus with good results, as is also reported more specifically in malignant insulinoma (1,10,13,14,15). In the patient with the de novo malignant insulinoma, stabilization occurred during 10 months when combined with a SSA. In 1/5 patients, everolimus was started after transformation of the pNET to a malignant insulinoma phenotype: the effect of everolimus remains unclear, because interruption was necessary for progressive thrombopenia only a couple weeks after therapy start. After dose reduction, everolimus had to be stopped again because of refractory edema and progressive disease. In 3/5 patients disease stabilization occurred for respectively 13 months, 13 months and 4.5 years.

3/5 patients were treated with sunitinib (a VEGF Tyrosine Kinase Inhibitor) at a dose of 37.5 mg each day: one patient maintained a stable disease during one year; for the second patient a dose reduction to 25 mg a day was necessary because of hand-foot syndrome grade 3, leucopenia and thrombopenia: a stable disease could be maintained during six months; in the third patient sunitinib had to be stopped for weight loss, vomitus and epigastralgia, although a stable disease was documented under this therapy. Kulke et al. showed in a multicenter phase II study that sunitinib is associated with antitumor activity in patients with advanced NETs and that the overall objective response rate is greater in patients with pNETs than with carcinoid tumors (16.7% versus 2.4%) (16). The median time to tumor progression exceeds 7 months in both patients groups (16).

In 4/5 patients, transarterial chemotherapy with intrahepatic doxorubicin beads was applied. In two patients liver failure, in part possibly related to drug toxicity, occurred with subsequent hepatic encephalopathy: one of them died only a few days after the last administration and another patient died one month after chemoembolization due to further disease progression. In the third patient, TACE prevented further hypoglycemic events after one administration though because of clinical deterioration with decay, no further treatment was possible. In the fourth patient, disease stabilization occurred during 14 months after the first administration of the intrahepatic doxorubicin beads and a partial disease response two months after the second administration could be documented. Data in literature suggest induction of partial remission in 40-60% of pNETs with liver metastases, although other authors documented rather poor results (9,17). However,

survival rates are better if the primary tumor is resected and if curation of metastatic liver disease is intended (9).

Radiofrequency ablation and cryoablation are preserved for small hepatic metastases (< 3 cm) of a well-defined NET (9,12).

As for SSA, PRRT also targets the somatostatin receptor (subtype 2) and is considered as one of the most successful treatments for metastatic pNETs that exhibit an intense expression of somatostatin receptors (11,13). Although the poorly differentiated character of the malignant insulinoma (proliferation index > 20%) in 3/5 patients, PRRT was administered at 8-wk intervals because of an intense somatostatin receptor expression on Ga-68 Dotatoc PET-CT scan. In the first patient, three cycles of ^{177}Lu octreotate were added to everolimus 5mg /day: after the third cycle radiological evaluation showed disease stabilization at the lymph nodes and liver, but also development of multifocal bone metastases. In the second patient, a hypoglycemic coma due to progressive disease appeared one month after the last of four cycles ^{90}Ytrium dotatoc. In the third patient, disease stabilization occurred only for two more months after four cycles ^{90}Ytrium dotatoc. In our patient cohort, a substantial positive effect on hypoglycemic events and outcome could not be established despite an intense somatostatin receptor expression, though in larger cohorts, PRRT has proven to be a very effective treatment (11) with prevention of hypoglycemia in 40-50% of the patients and partial tumor response (1). Different somatostatin receptor subtype expression between well, intermediate and high-grade pNETs can be a possible explanation for our observation (for example, unlike in well or intermediate pNETs, the expression of somatostatine receptor subtype 5 is present in high-grade pNETs, where SSA and PRRT predominately bind to subtype 2) (11).

Induction of remission in metastatic pNETs with conventional chemotherapy (streptozocin, doxorubicin or 5-fluorouracil) varies between 10 - 40% in older studies (1) (median duration of tumor response is 9.8 months) (18) and toxicity is significant (1): for these reasons, chemotherapy is generally not accepted as first-line treatment, though needs to be considered in a very aggressive disease. More recently, other small studies including platinum based chemotherapy have reported high response rates. Three of our patients received chemotherapy (1/3 patients doxorubicin-cyclophosphamide-cisplatin and 3/3 patients platinum-etoposide) with immediate disease progression in one of three patients and disease stabilization for four months and one year in the two others.

Hepatectomy and liver transplantation are performed in selected cases (2): it is exclusively preserved for young patients in a good general condition with liver limited disease and a well differentiated tumor with a low proliferation rate (1,2,9).

Despite various treatment options, the outcome of patients with a malignant insulinoma remains relatively poor (3) with a median survival period of approximately 2 years (6) and a 10-year survival ≤ 20% (13). Main determinants are resectability of the tumor and its biological behavior, rather than type of medical treatment (3, 6). Of all our five patients, only one is still alive: this patient is doing well with a stable disease 7 months after TACE. Four of five patients died 25, 17, 3 and 1 month(s) after diagnosis of the malignant insulinoma.

Conclusion

Due to rarity of malignant insulinomas, many questions concerning etiology, pathogenesis, determinants of disease course and best treatment strategy remain unanswered. However, poor prognosis and risk of a life-threatening hypoglycemic event, make a better understanding absolutely necessary. A challenge for the future is to identify underlying mechanisms of this disease entity and especially its biological behavior, since it is the major determinant to predict long-term survival. In this way, new therapeutic strategies and patient-tailored therapy can be achieved and improvement of diagnostic tools and outcome is possible.

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