

# Adult-onset nesidioblastosis: a challenging diagnosis revealed by glucagon-like-peptide-1 receptor imaging

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## Summary

A 52-year-old female presented with recurrent episodes of fasting or post-absorptive hypoglycemia. A 72-h fasting test confirmed endogenous hyperinsulinemia. Conventional imaging was unremarkable. Selective pancreatic arterial calcium stimulation and hepatic venous sampling showed a maximum calcium-stimulated insulin concentration from several pancreatic areas, mainly the proximal splenic artery and the proximal gastroduodenal artery, suggesting the presence of one or more occult insulinoma(s) in the region of the pancreatic body. <sup>68</sup>Ga-DOTA-exendin-4 PET/CT showed however generalized increased uptake in the pancreas and a diagnosis of nesidioblastosis was therefore suspected. The patient has been since successfully treated with dietetic measures and diazoxide. Treatment efficacy was confirmed by a flash glucose monitoring system with a follow-up of 7 months.

## Learning points

- Adult nesidioblastosis is a rare cause of endogenous hyperinsulinemic hypoglycemia.
- The distinction between insulinoma and nesidioblastosis is essential since the therapeutic strategies are different.
- <sup>68</sup>Ga-DOTA-exendin-4 PET/CT emerges as a new noninvasive diagnostic tool for the localization of an endogenous source of hyperinsulinemic hypoglycemia.
- Medical management with dietetic measures and diazoxide need to be considered as a valuable option to treat patients with adult nesidioblastosis.
- Flash glucose monitoring system is helpful for the evaluation of treatment efficacy.

## Background

Adult nesidioblastosis is a rare cause of endogenous hyperinsulinemic hypoglycemia. The cause is not known, but the recently observed association with gastric bypass surgery in obese patients suggests that a reactive process possibly unmasks or induces an alteration in  $\beta$  cell regulation, resulting in its hyperfunction (1).

The clinical and biochemical presentation of nesidioblastosis is the same as for insulinoma. The distinction between the two entities is essential since different therapeutic strategies are required. As conventional imaging fails to detect nesidioblastosis and occult insulinoma, selective pancreatic arterial calcium

stimulation (SACST) and glucagon-like-peptide-1 receptors (GLP-1R) imaging have emerged as new diagnostic tools.

The management of adult nesidioblastosis includes medical treatment with dietetic measures and diazoxide or pancreatectomy. The choice of treatment is based on limited experience related to case reports and small series.

## Case presentation

We report the case of a 52-year-old Caucasian female with no significant medical history except for a transient ischemic attack. She was taking only dietary supplements and had no chronic alcohol consumption. Her family history was significant for diabetes in her sister. Clinical examination was unremarkable. Especially, she showed no clinical sign of insulin resistance and the BMI was 19.1 kg/m<sup>2</sup>. In July 2020, she was brought to the emergency department for hypoglycemia (45 mg/dL; normal value > 60 mg/dL) after a physical effort. She had been experiencing episodes of dizziness for 2 years and low plasma glucose was confirmed on several blood tests. These episodes mostly occurred in fasting condition or a long time after meals, never in postprandial state, and were managed by a regular self-administration of carbohydrates. A fasting blood test done by her general practitioner revealed hyperinsulinemic hypoglycemia (low plasma glucose level of 35 mg/dL with an inappropriately elevated insulin concentration of 35.4 pmol/L; values in case of hyperinsulinemic hypoglycemia: plasma glucose < 55 mg/dL and insulin level ≥ 18 pmol/L) (2). She was referred to our hospital for further investigation.

## Investigation

Routine laboratory findings were normal including lipid profile and a morning cortisol level of 291 nmol/L (normal value: 130–500 nmol/L) which excluded adrenal insufficiency. A prolonged fasting test was terminated after 15 h because of symptomatic hypoglycemia confirmed by a low plasma glucose level (33 mg/dL) with inappropriately elevated level of insulin (30.8 pmol/L) and C-peptide (0.39 nmol/L). These results confirmed endogenous hyperinsulinemia (diagnostic values: plasma glucose < 55 mg/dL, insulin ≥ 18 pmol/L and C-peptide ≥ 0.20 nmol/L) (2). The plasma glucose level in response to 1 mg glucagon injection rose to 100 mg/dL and β-hydroxybutyrate levels were low at 0.40 nmol/L, indicating insulin-mediated hypoglycemia (expected values: plasma glucose increase > 25 mg/dL and β-hydroxybutyrate level ≤ 2.7

nmol/L) (2). Sulfonylureas and glinides were not detected in 24-h urine collection, and circulating insulin antibodies were not found.

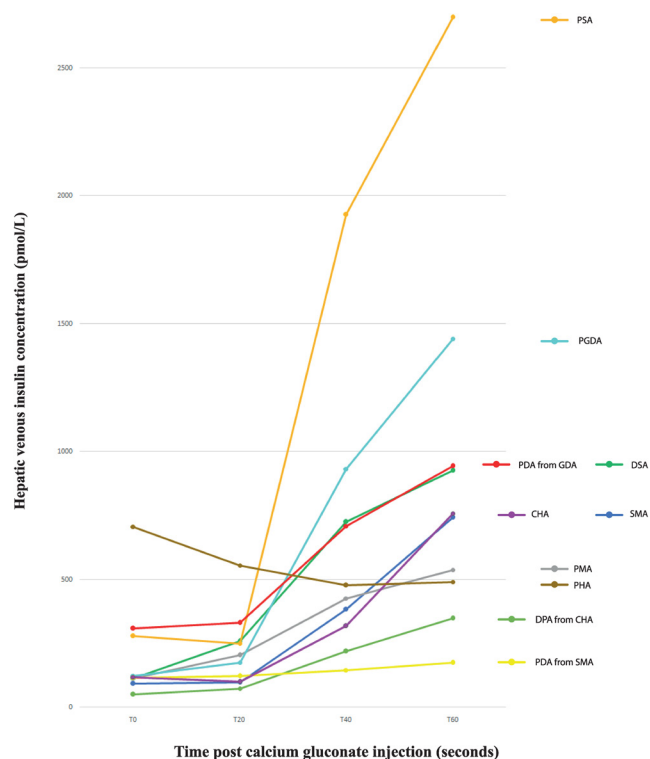
The etiology of endogenous hyperinsulinemia was further evaluated in order to exclude an insulinoma. Endoscopic ultrasonography, CT, MRI, and <sup>68</sup>Ga-Dotatate PET scan were unremarkable. SACST was performed to detect an occult insulinoma. This procedure demonstrated a marked increase (10-fold increase over the baseline) in hepatic venous insulin concentration after calcium injection in the proximal splenic artery and in the proximal gastroduodenal artery, considered to be the dominant arteries. Significant though smaller elevation of insulin secretion was also observed after calcium injection in the distal splenic artery (8-fold increase over the baseline) and in the pancreaticoduodenal artery arising from the gastroduodenal artery (3-fold increase over baseline) (Fig. 1). Taking into account the maximum stimulation of hepatic venous insulin concentration, the presence of an occult insulinoma in the region of the pancreatic body was suspected. A corporeo-caudal pancreatectomy was first proposed to the patient but denied given the expected complications after such a surgery. She next underwent a <sup>68</sup>Ga-DOTA-exendin-4 PET/CT (Fig. 2), which showed generalized, moderate increased uptake in the whole pancreas without relevant differences between the pancreatic sections (pancreatic head: SUV<sub>max</sub> 6.8/SUV<sub>mean</sub> 6.0; pancreatic body: SUV<sub>max</sub> 7.2/SUV<sub>mean</sub> 6.4; pancreatic tail: SUV<sub>max</sub> 7.3/SUV<sub>mean</sub> 6.4). There was no focal lesion indicative of insulinoma. A diagnosis of nesidioblastosis was therefore retained.

## Treatment

The patient was treated with diazoxide at the initial dose of 150 mg per day. She also followed a diet with a regular intake of carbohydrates throughout the day, mainly complex carbohydrates with slow absorption. We used the flash glucose monitoring (FGM) system to evaluate the therapeutic response.

## Outcome and follow-up

The treatment was well tolerated and significantly reduced hypoglycemic episodes during the day with persistent mild hypoglycemia during the night. The patient's quality of life improved and she could resume her professional activity. Interestingly, the patient undertook 13 days of FGM without diazoxide therapy. We evidenced an increase in hypoglycemic episodes, with



**Figure 1**

Results of the selective arterial calcium stimulation with hepatic venous sampling. The calcium injection was performed in the following order: SMA, superior mesenteric artery; DSA, distal splenic artery; PMA, pancreatica magna artery; PSA, proximal splenic artery; PGDA, proximal gastroduodenal artery; DPA from CHA, dorsal pancreaticoduodenal artery from common hepatic artery; PDA from SMA, pancreaticoduodenal artery from superior mesenteric artery; PDA from GDA, pancreaticoduodenal artery from gastroduodenal artery; CHA, common hepatic artery; PHA, proper hepatic artery. Catheters were inserted into both right hepatic vein, for blood sampling, and femoral artery, for access to the different arteries that vascularize the pancreas. Calcium gluconate (0.0025 mEq Ca/kg) diluted to a 5 mL bolus was injected into the 10 mentioned arteries. Blood sampling was obtained before the injection (baseline = T0), 20 (T20), 40 (T40), and 60 (T60) s after calcium injection.

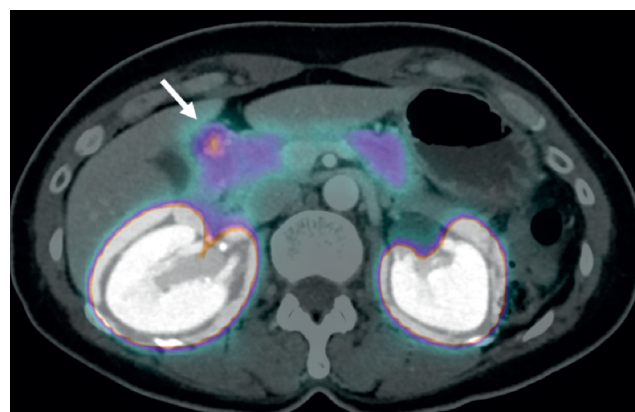
47% of values below 70 mg/dL (Fig. 3). In comparison, under treatment with 450 mg diazoxide, only 13% of values were below 70 mg/dL, mostly during the night (Fig. 4). The total length of follow-up is currently of 7 months and the same treatment is maintained.

## Discussion

Adult nesidioblastosis is a rare cause of endogenous hyperinsulinemic hypoglycemia and delayed diagnosis is common. The cause is not known, but the recently observed association with gastric bypass surgery in obese patients suggests that a reactive process possibly unmasks or induces an alteration in  $\beta$  cell regulation, resulting in its hyperfunction (1). It is not possible to

distinguish clinically and biochemically nesidioblastosis from occult insulinoma(s). Conventional imaging, including endoscopic ultrasonography, CT, and MRI fail to diagnose both entities. In such cases, current recommendations suggest the use of SACST, a minimally-invasive procedure (3).

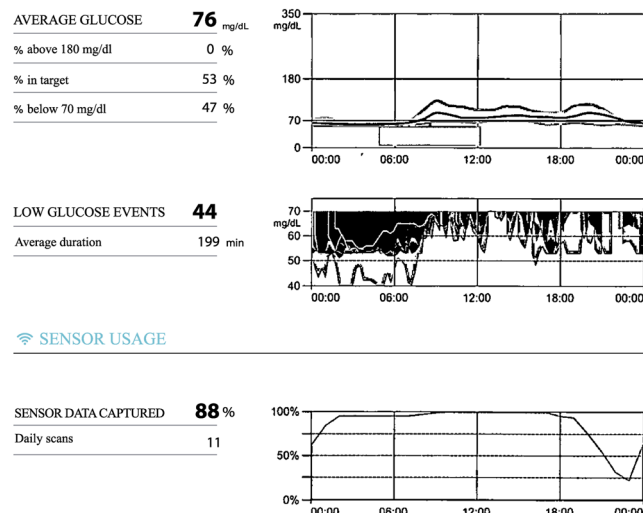
SACST is based on the fact that calcium stimulates the release of insulin from hyperfunctioning, abnormal pancreatic  $\beta$  cells, but not from normal  $\beta$  cells. Therefore, at least a twofold increase in hepatic venous insulin concentration over baseline following calcium injection into a single pancreatic artery is considered the criteria to localize an occult insulinoma (4) with high sensitivity (67–100%) (5). Positivity in more than one artery at SACST may be suggestive of diffuse nesidioblastosis, but will not reliably differentiate between nesidioblastosis and insulinoma, particularly in the presence of multiple tumors, such as in multiple endocrine neoplasia type 1, or in the case of overlapping pancreatic arterial distributions. In the study of Thompson *et al.*, 75% of patients with diffuse nesidioblastosis and 25% of patients with insulinoma demonstrated positivity in two or more pancreatic arterial distributions at SACST (4). Also, patients with larger elevation of the hepatic venous insulin concentration in one arterial distribution are much more likely to benefit from pancreatic exploration than patients with small increases in multiple arterial distribution (4). In our case, according to the SACST results showing a major gradient in the proximal splenic artery and the proximal



**Figure 2**

Axial reconstruction of contrast-enhanced  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT. There is typical uniform uptake in the pancreas (pancreatic head:  $\text{SUV}_{\text{max}} 6.8/\text{SUV}_{\text{mean}} 6.0$ ; pancreatic body:  $\text{SUV}_{\text{max}} 7.2/\text{SUV}_{\text{mean}} 6.4$ ; pancreatic tail:  $\text{SUV}_{\text{max}} 7.3/\text{SUV}_{\text{mean}} 6.4$ ) without focal intra-pancreatic uptake. The actual image shows parts of the pancreatic head and the pancreatic tail. There is focal extra-pancreatic uptake located in the adjacent duodenum, corresponding to Brunner glands (arrow), which is a known pitfall and should not be mistaken for pathology (14).

## GLUCOSE



**Figure 3**

Flash glucose monitoring without diazoxide in adult nesidioblastosis.

gastroduodenal artery, a corporeo-caudal pancreatectomy was first considered. It is, however, important to have a confirmation of the precise source of hormone secretion with another investigation given the expected complications after such surgery.

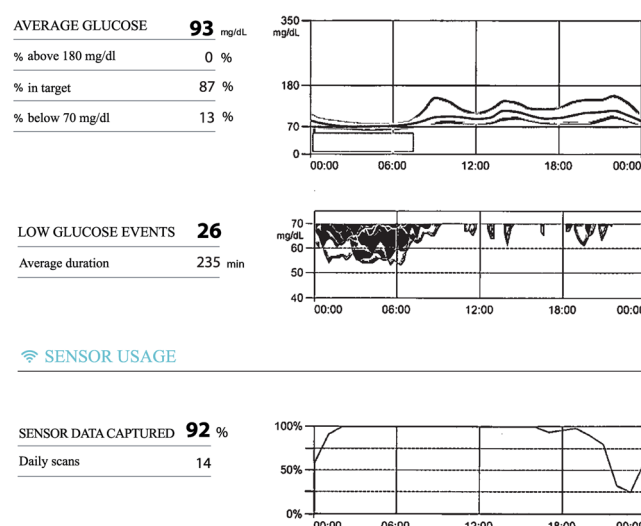
*In vitro* studies have shown a higher density of GLP-1R in benign insulinomas compared to normal  $\beta$  cells (6). Novel radiotracers (indium-111, technetium-99m, or gallium-68-labeled-exendin-4) targeting these receptors have emerged as noninvasive diagnostic tools for imaging  $\beta$  islet cell pathology. Wild *et al.* proposed an algorithm for the assessment of endogenous hyperinsulinemic hypoglycemia in which GLP-1R imaging is indicated if no lesion is visible on conventional CT or MRI of the pancreas (7). We believe however that endoscopic ultrasonography of the whole pancreas is also essential in the first diagnostic tree, as it is more sensitive to detect small neuroendocrine tumors (8) and may allow a cytologic confirmation. Nevertheless, a recent prospective study showed a very high sensitivity of  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT to detect insulinomas (94.6%) (imaging technique used in our case) and this sensitivity was higher than that observed with  $^{111}\text{In}$ -DOTA-exendin-4 SPECT/CT (9). Interestingly, the density of GLP-1R in nesidioblastosis is higher than in the normal pancreas but lower than in benign insulinoma (6). Likewise, Christ *et al.* reported a generalized moderate increase of the  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT uptake ( $\text{SUV}_{\text{max}}$  6.9) in a recent case study of nesidioblastosis (10). This implies that GLP-1R

imaging could be able to differentiate between occult insulinoma and diffuse nesidioblastosis.

Accurate diagnosis is essential since different therapeutic strategies are required, ranging from endoscopic ultrasound-guided radiofrequency ablation or enucleation in the case of insulinoma to partial pancreatectomy in focal nesidioblastosis (11). In our case, the  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT played an essential role in the diagnosis of diffuse nesidioblastosis sparing the patient from a corporeo-caudal pancreatectomy. Unfortunately, GLP-1R imaging is available only in specialized centers.

The choice of treatment in adult nesidioblastosis is based on limited experience relying on case reports and small series. Until now, most patients were diagnosed with nesidioblastosis after surgery that had been performed for suspected insulinoma. Partial pancreatectomy (60–80% resection of the pancreatic tissue) controls nesidioblastosis in 50% of patients without additional medication, especially in focal forms (12). As pancreatectomy is associated with significant comorbidity (diabetes and exocrine insufficiency), medical treatment could be preferred especially in cases of diffuse nesidioblastosis. Diazoxide is the most frequently used medical treatment combined with dietetic measures. It reduces insulin release by pancreatic  $\beta$  cells through binding to the SUR1 domain which opens the K+ATP channel. Diazoxide is rarely used as the first therapy for nesidioblastosis because the diagnosis is mostly made post-operatively.

## GLUCOSE



**Figure 4**

Flash glucose monitoring during diazoxide treatment in adult nesidioblastosis.

In the literature, only a small series of four patients was successfully treated primarily with diazoxide for nesidioblastosis as all patients were considered inoperable (13). The dosage varied from 225 to 300 mg per day with a follow-up of 34–40 months.

In our case, the success of the treatment was assessed by an FGM system with a final dose of 450 mg during a follow-up of 7 months. To our knowledge, this is the first case of nesidioblastosis where the treatment with diazoxide was evaluated with the help of a glucose monitoring system. Even if the recording of interstitial glucose concentrations is less reliable for low values, the 13 days of FGM without diazoxide therapy confirmed the efficacy of the treatment. The main side effects of diazoxide are nausea and vomiting, especially at the beginning of treatment, hypertrichosis and water retention. Our patient did not experience any side effects so far.

Nesidioblastosis is a histopathological diagnosis and pancreatectomy or biopsy was not performed in the present case. Therefore, in theory, one cannot completely exclude that a very small insulinoma was present undetectable using  $^{68}\text{Ga}$ -DOTA-exendin-4-PET/CT since the spatial resolution of the PET is approximately 4–6 mm. However, in this case, the treatment would not have differed.

In conclusion, the distinction between clinically localizable insulinoma and nesidioblastosis is essential since the therapeutic strategies are different.  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT emerges as a new noninvasive diagnostic tool and was a critical investigation in our case. For patients who feature clear endogenous hyperinsulinemia,  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT without focal lesion, and SACST with insulin secretion in two or more arteries, adult nesidioblastosis should be strongly considered.

#### 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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#### Patient consent

Written informed consent was obtained from the patient for publication of this article and images.

#### Author contribution statement

S Demartin wrote the case report. RM Furnica, D Maiter and E Christ critically reviewed and corrected the manuscript. P Goffette performed and reviewed the results of the SACST. MT Freitag performed the  $^{68}\text{Ga}$ -DOTA-exendin-4 PET/CT, evaluated the imaging data and reviewed the final manuscript.

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