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ORIGINAL ARTICLE

Role of ^{68}Ga somatostatin receptor PET/CT in the detection of endogenous hyperinsulinaemic focus: an explorative study

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Abstract

Purpose To explore the role of ^{68}Ga-DOTATATE/DOTATOC PET/CT (SR PET/CT) in patients with suspicion of or histopathologically proven pancreatogenic hyperinsulinaemic hypoglycaemia.

Methods We included 13 patients with histopathologically proven or a high clinical suspicion of pancreatogenic hyperinsulinaemia. All the patients underwent a SR PET/CT scan. The results were correlated with histopathological findings. Normalization of blood glucose levels after resection of the pancreatic lesion, as well as a cytological and/or pathological diagnosis of insulinoma, was considered the diagnostic gold standard for insulinoma. The diagnosis of nesidioblastosis was based on exclusion of an insulinoma and conclusive pathological examination of a segment of the pancreas. Malignant insulinoma was defined as the presence of locoregional or distant metastases.

Results Based on histopathology, 13 patients were found to have pancreatic hyperinsulinaemia: two patients had malignant insulinoma, eight had nonmetastasized insulinoma, and three had nesidioblastosis. SR PET was positive in 11 of the 13 patients (84.6 %) with a final diagnosis of endogenous pancreatic hypoglycaemia. Histopathological staining confirmed 16 foci of hyperinsulinism (insulin positivity). SR PET detected 14 of the 16 lesions, resulting in a sensitivity of 87 %. One intrapancreatic spleen was falsely diagnosed as insulinoma focus on SR PET, resulting in positive predictive value of 93.3 %. Immunohistochemical staining of somatostatin receptor (SSR) subtype 2a was available in ten specimens: two nesidioblastosis, and seven benign and one malignant insulinoma. Eight out of the ten specimens (80 %) stained strongly to moderately positive. Seven of the eight SSR2a-positive lesions were picked up on SR PET. Based on the results of SR PET/CT, nine patients achieved complete remission of the hypoglycaemic events during follow-up.

Conclusion This explorative study suggests that SR PET in combination with CT may play a significant role in the detection and management of patients with pancreatogenic hyperinsulinaemic hypoglycaemia. A large proportion of insulinomas express SSR2a, and a larger study is needed to fully assess the diagnostic accuracy of SR PET in patients with insulinoma and nesidioblastosis compared with current localizing studies used in clinical practice.

Keywords Insulinoma · Nesidioblastosis · Somatostatin receptor · PET/CT · ^{68}Ga-DOTATATE · ^{68}Ga-DOTATOC

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Introduction

Insulinoma is a rare neuroendocrine tumour (NET) producing an excessive amount of insulin with an incidence of 1 – 3 per million per year [1, 2]. About 97 % of insulinomas are located within the pancreatic parenchyma, approximately 10 % are multiple and 5 – 10 % are associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome. Malignancy can be expected in less than 10 % of patients and more frequently in those with tumours >2 cm [3, 4]. Patients with insulinoma and noninsulinoma pancreatogenic hypoglycaemia syndrome (NIPHS), also referred to as adult nesidioblastosis, suffer from severe hypoglycaemia due to inappropriately increased levels of circulating plasma insulin or proinsulin. The clinical diagnosis can be made by a positive 72-h fasting test demonstrating nonsuppressed plasma insulin, proinsulin, and/or C-peptide levels in the presence of hypoglycaemia. Factitious use of oral blood glucose-lowering drugs should always be excluded [5–7].

The role of imaging is to detect and provide precise anatomical localization and staging of the tumour prior to surgery [8]. Accurate preoperative localization of an insulinoma is desirable because some tumours may not be palpable at the time of surgery. However, due to their small size and similarity to surrounding tissue, localization may be a challenging clinical problem. Conventional imaging with gadolinium-enhanced MRI; three-phase CT and endoscopic ultrasonography (EUS) are the three preferred imaging modalities [8]. Three-phase CT has a sensitivity of 30 – 85 % depending upon the size of the insulinoma [9]. When combined with EUS, the sensitivity may increase to 100 % [10]. MRI has a sensitivity in the range 85 – 95 % in the detection of insulinomas and their metastases [11]. EUS has the highest sensitivity of 94 %. The high spatial resolution allows detection of very small lesions. The sensitivity of the technique, however, is lower if the lesions are located in the tail of the pancreas [12].

The role of somatostatin receptor (SSR) imaging with [111]In Octreoscan for the detection of hyperinsulinaemic focus is a matter of controversy, with some reports suggesting that the sensitivity of SSR imaging is about 50 – 60 % and others suggesting a much lower sensitivity of 24 % [13, 14]. This lower sensitivity can primarily be attributed to the limited spatial resolution of scintigraphy techniques, particularly if the lesion is less than 1 cm in diameter. Immunohistochemistry (IHC) as well as reverse transcription polymerase chain reaction (RT-PCR) have, however, shown the presence of SSR subtypes 2a and 5 in abundance on insulinomas. The degree of expression of SSR subtypes is, however, largely dependent on tumour aggressiveness, i.e. the levels of expression of SSR2a and SSR5 are higher in more aggressive tumours [15]. Previous studies in various classes of NET have shown a very good correlation between IHC and RT-PCR and the degree of SSR expression assessed in vivo using ^{68}Ga-labelled SSR PET (SR PET) [16–19]. In general, the combination of three-phase CT and ^{68}Ga-DOTATATE/DOTATOC PET provides significantly better diagnostic accuracy particularly in staging and restaging as it picks up distant metastases in a single imaging session [20].

With this background we performed a retrospective analyses to (a) determine the sensitivity of ^{68}Ga-DOTATATE/DOTATOC PET/CT for localizing the focus of endogenous hyperinsulinaemia in the pancreas, (b) determine the level of SSR2a expression in insulin-producing foci, and (c) explore the impact of SR PET on patient management.

Materials and methods

Data search and patient selection

The inclusion criteria for this retrospective analysis were (a) patients with histopathological, clinical or biochemical confirmation of insulinoma, and (b) patients who had not undergone pancreatectomy prior to the PET/CT examination. All patients sent to the Department of Nuclear Medicine, Campus Virchow-Klinikum, Charité Universitätsmedizin, Berlin, for ^{68}Ga-DOTATOC/DOTATATE PET/CT were screened for the indication. Overall 18 patients had been examined with PET/CT with a high degree of suspicion or histopathologically confirmed endogenous hyperinsulinaemia. Out of these 18 patients, 13 met the inclusion criteria.

Immunohistochemistry

For IHC, 4-μm formalin-fixed, paraffin-embedded tissue sections were immunostained using heat-induced epitope retrieval, the Ventana Benchmark XT platform (Ventana Medical Systems, Tucson, AZ), the Ultraview DAB detection system (Ventana), and synaptophysin (clone 27G12, 1:50; Leica Biosystems), and chromogranin A (CgA, clone LK2H10, prediluted, Ventana Medical Systems). IHC for SSR2a was performed after pretreatment with protease using a rabbit monoclonal antibody directed against SSR2a (clone EP 149, also known as UMB-1; Epitomics, Burlingame, CA). For visualization, the iView DAB detection kit (Ventana) was used. The IHC results were reported as 'negative' (no positive cells), or 'positive' (at least 20 % of cells positive). The staining intensity was interpreted according to the method of Volante et al. [21]. In addition, all the histopathological specimens were stained for insulin and proinsulin. IHC of CgA and synaptophysin is required to confirm the presence of NET, Ki67 is required for grading, and insulin and proinsulin IHC is required to confirm the presence of insulin-producing cells.

Assessment of endogenous hyperinsulinaemia

Normalization of blood glucose levels after resection of the pancreatic lesion, as well as cytological and/or pathological

diagnosis of an insulinoma, was considered the diagnostic gold standard for insulinoma. The diagnosis of nesidioblastosis was based on the presence of endogenous hyperinsulinaemia during hypoglycaemia and the exclusion of an insulinoma and/or conclusive pathological examination of a segment of the pancreas. Malignant insulinoma was defined as the presence of locoregional or distant metastases.

Imaging protocol

[68]Ga was eluted from a [68]Ge/^{68}Ga generator and labelled with either DOTATATE (six patients, from 2010 to June 2013) or DOTATOC (seven patients) according to the respective standard labelling procedure described elsewhere [22]. The selection of either DOTATATE or DOTATOC for imaging was purely based on the availability of the compound due to patent regulations. ^{68}Ga-DOTATATE/DOTATOC PET/CT was performed according to EANM guidelines: after injection of 110 MBq of the radiotracer imaging was performed 60 min after injection [23]. Until June 2010, PET/CT was performed using a Biograph 16 PET/CT system (Siemens AG, Germany) with 120 kV, 230 mAs, five or six bed positions each with an acquisition time of 3 min, collimation of 0.75 mm and slices of $16 \times 9 \times 0.75$ mm. After June 2010 all PET scans were acquired in three-dimensional mode using a Gemini TF 16 PET/CT system (Philips Medical Systems). The standard 3D-LOR algorithm of the system software was used with default parameter settings to reconstruct transaxial slices of 144×144 voxels of $4.0 \times 4.0 \times 4.0$ mm. In all patients, a low-dose CT scan acquired immediately before the PET scan was used for attenuation correction (120 kVp, 30 mAs). If contrast-enhanced CT was performed, 70 – 100 ml Ultravist 370 (Bayer Schering Pharma, Berlin, Germany) with a delay of 30 s for the arterial phase, 50 s for the portovenous phase and 70 s for the venous phase was injected intravenously, and images were acquired using bolus tracking methodology.

Images were analysed independently, unblinded, by two nuclear medicine physicians (V.P., T.D.). Any circumscribed focal tracer uptake in the pancreas more than that of the surrounding tissue was considered pathological on PET images. In addition, the maximum standardized uptake value (SUVmax) for each suspicious lesion was also documented. Because of the known influence of size on SUV, particularly for lesions <1 cm in size, no SUV-based cut-off was used for differentiating between normal and pathological uptake.

Results

Demographics

This explorative retrospective analysis included 13 adult patients (mean 53.1 years, range 14–80 years, 4 men, 9 women;

Table 1) with histologically proven endogenous hyperinsulinaemic hypoglycaemia. Three patients had MEN-1 syndrome. The results of the 72-h fasting test were retrieved from each patient's file. The test was positive in eight patients, negative in two and was not performed in the remaining three.

Somatostatin receptor PET/CT

Table 1 summarizes the patient characteristics and fasting test results. Based on pathological results, three patients had nesidioblastosis, two had malignant insulinomas, and the remaining eight had benign insulinoma. SR PET was positive in 11 patients (84.6 %; Table 2). In the remaining two patients, the focus was confirmed on selective intraarterial calcium stimulation test. SR PET showed multiple (seven) SSR-positive lesions in the pancreas in three patients with adult onset nesidioblastosis. In all the patients, the lesions were located near the ductus pancreaticus (size range 8 – 11 mm; Fig. 1).

Immunohistochemistry

All lesions were positive on IHC for synaptophysin and CgA, suggesting neuroendocrine differentiation. The Ki67 proliferation rate was in the range 1 – 20 %. Histopathological staining of insulin confirmed 15 of 16 foci of hyperinsulinism. The remaining lesion was an intrapancreatic spleen. SR PET correctly detected 14 of 16 lesions resulting in a sensitivity of 87.5 %. One intrapancreatic spleen was falsely diagnosed as an insulinoma focus on SR PET resulting in positive predictive value of 93.3 %. IHC staining of SSR2a could only be performed on ten histopathological specimens (two nesidioblastosis, seven benign and one malignant insulinoma); the other six specimens could not be stained due to lack of sufficient tissue material. Eight out of the ten specimens (80 %) showed SSR2a positivity on IHC whereas two (20 %) were negative. Of the eight specimens positive for SSR2a on IHC, six (75 %) showed 3+ staining, and two (25 %) were moderately positive. SR PET detected seven of eight (88 %) of the SSR2a-positive lesions. In two hyperinsulinaemic foci negative on SR PET, IHC was negative for SSR2a in one and intensely positive (3+) in another patient. Example ^{68}Ga-DOTATATE PET/CT imaging in the detection of insulinoma in a 49-year-old female patient is shown in Fig. 2.

Standardized uptake value and tumour size

The mean SUVmax and standard deviation of the lesions and normal pancreas were 12 ± 10.3 (range 3 – 42.9) and 3.8 ± 1 (1.9 – 5.3). The mean target (lesion) to nontarget (normal pancreas) ratio was 2.9 ± 2.4 (range 1.5 – 10.3) respectively. Three-phase CT and MRI detected 12 of 16 hypervascular lesions; their sizes were in the range 5 – 11 mm. One of the lesions was an intrapancreatic spleen.

Table 1 Patient characteristics

Patient no.	Age (years)	Sex	Indication for somatostatin receptor PET/CT	MEN-1	Fasting test	Clinical course after imaging	
						Treatment after imaging	Remission status
1	61	F	Suspicion	No	+	Distal pancreatectomy	CR
2	34	M	Suspicion	No	+	Total enucleation	CR
3	53	M	Suspicion	No	Not done	Distal pancreatectomy	CR
4[a]	67	F	Suspicion	No	−	Distal pancreatectomy	CR
5	18	F	Malignant insulinoma	Yes	Not done	Chemotherapy	PD
6	80	M	Malignant insulinoma	No	+	Diazoxide	SD
7	67	F	Nesidioblastosis	No	Not done	Lanreotide	SD
8[a]	51	F	Suspicion	No	+	Total enucleation, partial distal pancreatectomy	CR
9	49	F	Suspicion	No	+	Total enucleation	CR
10	17	F	Suspicion	Yes	+	Distal pancreatectomy	CR
11	72	F	Suspicion	No	+	Sandostatin LAR 20 mg	SD
12[a]	14	M	Suspicion	Yes	−	Distal pancreatectomy	CR
13	52	F	Suspicion	No	+	Distal pancreatectomy + splenectomy	CR

CR complete remission, PR partial remission, SD stable disease, PD progressive disease

[a] Positive calcium stimulation test

Clinical course after imaging

Based upon the results of SR PET/CT, nine patients achieved complete remission of hypoglycaemic events during follow-up (Table 1). In two patients SR PET showed a solitary SSR-positive lesion in the pancreas. Both the patients refused surgery and were treated with somatostatin analogue resulting in successful control of hypoglycaemic symptoms for more than 2 years. In one patient, SR PET showed a low tumour burden in the liver.

The patient had multiple comorbidities and was treated with diazoxide. During a follow-up of 7 months the patient was well controlled with morphologically stable metastases in the liver.

Discussion

Insulinoma is a rare NET, usually solitary and almost exclusively localized to the pancreas. The diagnosis can be made by

Table 2 Correlation between imaging and immunohistochemistry

Patient no.	CT abdomen[b]	Somatostatin receptor PET		Immunohistochemistry				Final diagnosis
		Result	Peptide	Ki67 (%)	Insulin	Proinsulin	SSTR2a	
1	+	+	DOTATOC	1	+	+	3+	Nesidioblastosis
2	+	+	DOTATOC	20	+	−	−	Benign insulinoma
3	+	+	DOTATOC	2	+	Mildly +	3+	Benign insulinoma
4	+	+	DOTATATE	1	+	+	3+	Nesidioblastosis
5	+	+	DOTATATE	2	+	+	3+	Malignant insulinoma
6	+	+	DOTATATE	5	+	+	NP	Malignant insulinoma
7	+	+	DOTATATE	2	+	NP	NP	Nesidioblastosis
8[a]	−	−	DOTATATE	3	+	Mildly +	3+	Benign insulinoma
9	−	+	DOTATATE	1	+	−	2+	Benign insulinoma
10	+	+	DOTATOC	5	+	+	2+	Benign insulinoma
11	+	+	DOTATOC	NA	+	NP	NP	Benign insulinoma
12[a]	−	−	DOTATOC	NA	+	Mildly +	−	Benign insulinoma
13	+	+	DOTATOC	1	+	+	3+	Benign insulinoma

NA not available, NP not performed

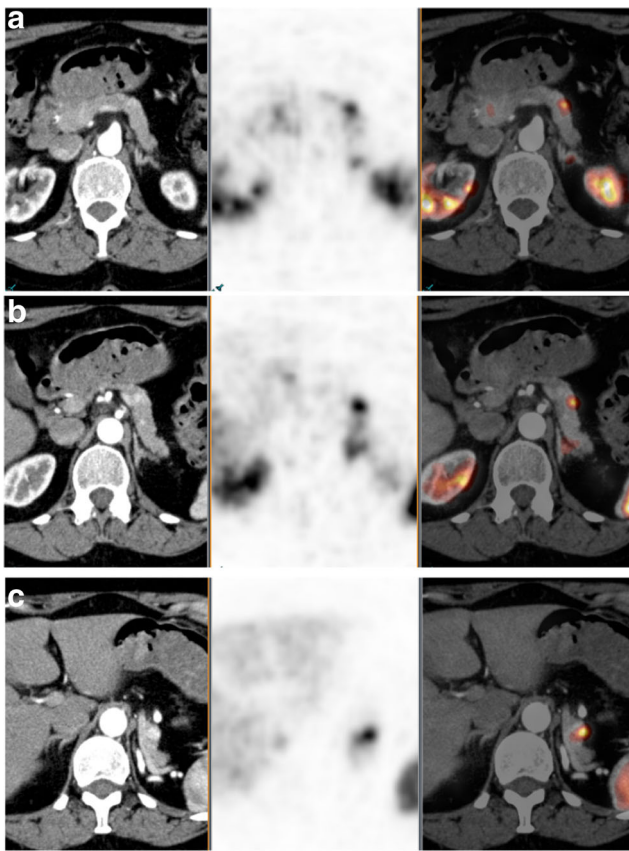[a] False-negative

[b] Non-contrast-enhanced CT

Fig. 1 Example ^{68}Ga-DOTATOC PET/CT imaging in a 61-year-old patient with nesidioblastosis. Three hypervascular lesions are detected in the tail of the pancreas, all near the ductus pancreaticus. The patient underwent distal pancreatectomy. Immunohistochemistry showed Ki67 of 1 %, positive staining for insulin, proinsulin and CgA, as well as synaptophysin. The patient was relieved of hypoglycaemic symptoms after the operation

demonstrating nonsuppressed plasma insulin, proinsulin and/or C-peptide concentrations in the presence of hypoglycaemia during a 72-h fasting test. The standard therapy for benign insulinoma is curative surgical resection. After endocrine diagnosis, imaging using various techniques is used to localize the tumour and rule out metastatic disease. As insulinomas are characteristically small, with approximately two thirds <2 cm at presentation, precise anatomical localization may be difficult [1, 2, 7].

Several somatostatin analogues including ^{68}Ga-DOTANOC, ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC have been developed for PET imaging and are now increasingly used in the diagnostic management of NET [17, 18]. These new compounds offer several advantages compared to somatostatin receptor scintigraphy (SRS). First, PET/CT has a higher spatial resolution than SRS and the combined anatomical and functional information obtained with the hybrid PET/CT technique results in higher sensitivity. Second, many of these radiotracers have a better affinity for SSR2 than [111]In Octreoscan. In addition, DOTATOC and DOTANOC cover a broader spectrum of SSRs than [111]In Octreoscan.

In our study, SR PET/CT demonstrated a high sensitivity (85 %) in the detection of pancreatic foci responsible for endogenous hypoglycaemia. IHC validation of the presence of SSR2a in 80 % of the insulin-producing foci supports the use of SR PET for detection of pancreatogenic insulin-producing foci. The high detection rate of SR PET in this study in comparison to historical data on SRS may be due to the higher affinity shown by ^{68}Ga-labelled analogues for SSR subtypes 2, 3 and 5. ^{68}Ga-DOTATATE has a very high affinity for SSR2, even surpassing the binding affinity of natural somatostatin. Although the binding affinity for other SSR is low, it is higher than that of ^{111}In-pentetreotide [24]. The SSR density is different in benign and malignant insulinomas and some authors have reported a higher expression of SSR5 in malignant insulinomas [15]. It has also been reported that despite the variability of the SSR subtype expression in insulinomas, SSR4 is the subtype most frequently expressed in both benign and malignant insulinomas [25]. In our analysis, we did not use ^{68}Ga-DOTANOC PET/CT, but because ^{68}Ga-DOTANOC covers a broader spectrum of SSR (subtypes 2, 3 and 5), future studies should be performed to identify the role of ^{68}Ga-DOTANOC PET/CT in both malignant and benign insulinomas.

Interestingly the preliminary results suggest that ^{68}Ga-DOTANOC PET has a limited role in the detection of primary tumour in patients with clinical and biochemical suspicion of insulinoma, with a sensitivity of only 25 % [26]. In contrast, ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC showed a reasonably good sensitivity compared with ^{68}Ga-DOTANOC that could have been because of better tracer kinetics with a higher target to nontarget ratio [27]. In addition we defined a lesion on PET as positive based on visual assessment of uptake in comparison to that of the local surrounding pancreatic tissue, whereas Sharma et al. [26] used normal liver as the reference. The higher lipophilicity of ^{68}Ga-DOTANOC leads to higher uptake in the liver compared with ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE [27]. This is the reason we suggest that normal pancreas should be used as the reference for the detection of pancreatic lesions. We found mild to high uptake in the primary lesion as compared to the surrounding tissue with target to nontarget ratios in the range 1.5 – 10.3. The lesions ranged in size from 5 to 11 mm, and morphological imaging missed only few lesions; the latter could be probably because of slight differences in contrast phases of CT acquired on two different scanners.

In comparison with historical data on EUS in insulinoma, in this study SR PET was found to be less sensitive (85 % vs. 94 %). Despite this lower sensitivity, SR PET allows whole-body staging in one session, and when combined with three-phase CT, could potentially have a direct impact on the surgical resection or on choice of medical treatment as shown in our patient cohort in which 9 of 13 patients achieved complete remission of hypoglycaemic events during follow-up.

Fig. 2 a Example ^{68}Ga-DOTATATE PET/CT imaging in a 49-year-old female patient (patient 9) with insulinoma. A solitary intense SSTR-positive lesion is seen in the pancreas head with a high SUVmax (12.7). The patient underwent enucleation which led to complete remission of hypoglycaemic features. **b** Immunohistochemistry of the same patient as in **a** shows positive staining for somatostatin receptor (SSTR) 2a, insulin, CgA and synaptophysin, and is negative for proinsulin. The proliferation rate of the tumour was found to be 1 %
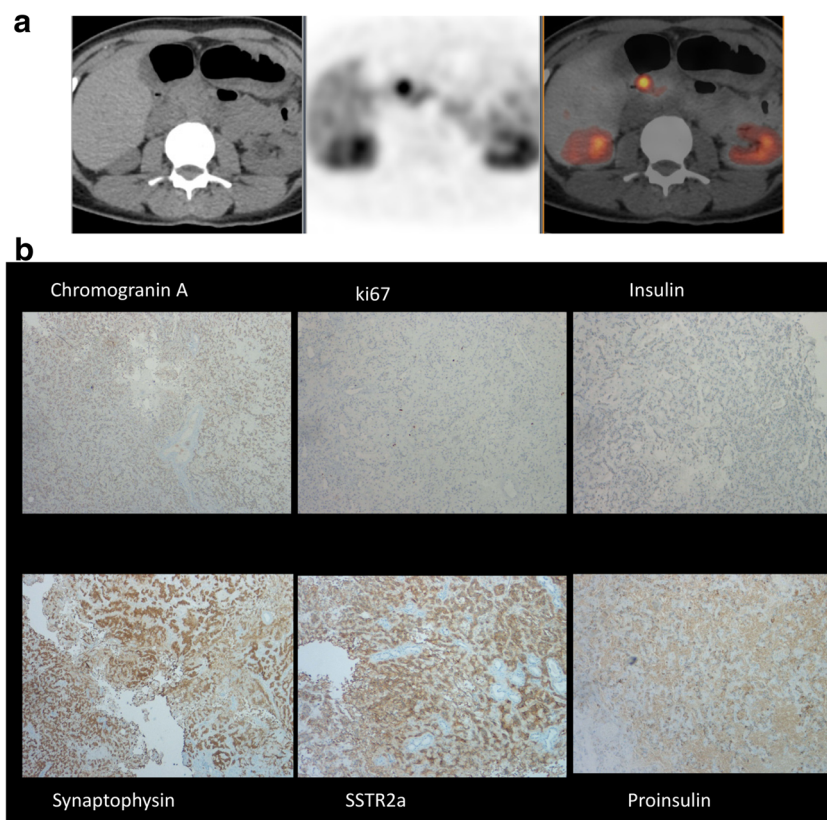
Whereas the treatment of choice for benign solitary insulinoma is enucleation of the tumour or partial pancreatectomy, for malignant insulinoma the presence of distant metastases changes the treatment strategy. The advantage of PET is in its ability to detect multifocal disease that may occur in up to 10 % of patients, and metastatic disease that occurs in another 10 % of patients. In patients showing distant metastases, high expression of SSR on malignant insulinoma could be used for peptide receptor radionuclide therapy.

On the other end of the spectrum of beta cell diseases of the pancreas is NIPHS. NIPHS is a rare syndrome, characterized by endogenous hyperinsulinaemic hypoglycaemia that is not caused by an insulinoma. Pancreatic specimens from such patients show beta cell hypertrophy, islets with enlarged and hyperchromatic nuclei, and increased periductular islets [28–30]. These histological findings are characteristic features of nesidioblastosis, a term that refers to neoformation of islets of Langerhans from the pancreatic duct epithelium. Localization studies are necessary to distinguish between insulinoma and diffuse islet cell hyperplasia. The disorder was first described by Laidlaw [31]. The diagnosis of nesidioblastosis is considered complex as conventional imaging studies are not helpful and questioning of the patient may reveal a history with a confusing pattern of symptoms. Selective arterial calcium stimulation with hepatic venous sampling has been utilized in some clinical centres to aid the diagnosis [29, 30]. In our study, three patients with NIPHS

showed multiple SSR-positive lesions on SR PET. All the patients showed intense SSR2a IHC staining. The presence of SSR in adult nesidioblastosis warrants further exploration of the role of SR PET in the management of patients with NIPHS [32, 33]. It would also be interesting to look into the role of ^{18}F-DOPA PET in the management of patients with adult nesidioblastosis as it has a definite role in the management of children with congenital hyperinsulinism.

Detection of differential SSR expression in insulinoma may sometimes be a problem on SR PET with tracers directed towards SSR2a. Reubi et al. have extensively looked into the SSR on insulinomas using autoradiography techniques, with mixed results. Although conventional imaging including EUS allows detection in the majority of patients there remains an unmet medical need to correctly localize the insulin-producing focus as uncontrolled severe hypoglycaemia is a life-threatening process. Wild et al. reported the first use in humans of ^{68}Ga-labelled or ^{111}In-labelled [Lys(40)(Ahx[6-aminohexanoic acid]-DOTA-(111)In)NH(2)]-exendin-4, a glucagon-like peptide-1 (GLP-1) receptor analogue, to potentially improve the detection of insulinomas [34]. GLP-1 is an intestinal hormone that stimulates insulin secretion through receptors expressed in islet cells. GLP-1 receptors are massively expressed in benign insulinomas. Recent studies have demonstrated that a radiolabelled GLP-1 analogue can detect occult insulinomas, which cannot be localized by other imaging modalities. However, in comparison to SR PET, GLP-1 scintigraphy has been found to have lower

sensitivity in the detection of malignant insulinomas. According to Wild et al., this observation is clinically relevant as SSR2 imaging can be recommended before surgery or peptide receptor radionuclide therapy when a malignant insulinoma is suspected [34–37]. It would be interesting to directly compare GLP-1 imaging and the more commonly available SR PET in the detection of pancreatic hyperinsulinaemic foci, particularly in those patients who are negative on SR PET or show multiple SR-positive lesions, e.g. MEN-1 patients.

Limitations of the study and future scope

The main limitations of the study were its retrospective design and small population size. Furthermore, PET/CT was performed on two different scanners with two different peptides, DOTATATE and DOTATOC, which could have independently affected the SUVmax of lesions. In addition, in retrospective studies of three-phase CT, the perfusion pattern may be quite heterogeneous because of the lack of strict timing for bolus tracking. This could have been the reason for CT missing some of the lesions seen on PET alone. It would have been interesting to have all the specimens stained with SSR2a antibodies, but this was technically not possible.

Conclusion

This explorative study suggests that SR PET can play a significant role in the detection and management of patients with pancreatogenic hypoglycaemia. A large proportion of insulinomas express SSR2a. A future study with a larger number of patients is needed to fully assess the accuracy of SR PET in patients with insulinoma and nesidioblastosis in comparison with localizing studies currently used in clinical practice.

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