Original Article

Noninvasive Diagnosis of Focal Hyperinsulinism of Infancy With [^{18}F]-DOPA Positron Emission Tomography

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Congenital hyperinsulinism of infancy (CHI) is characterized by severe hypoglycemia due to dysregulated insulin secretion, associated with either focal or diffuse pathology of the endocrine pancreas. The focal condition is caused by a paternally inherited mutation in one of the genes encoding the subunits of the β-cell ATP-sensitive potassium channel (SUR1/*ABCC8* or Kir6.2/*KCNJ11*) and somatic loss of maternal 11p15 alleles within the affected area. Until now, preoperative diagnostics have relied on technically demanding and invasive catheterization techniques. We evaluated the utility of fluorine-18 L-3,4-dihydroxyphenylalanine ([^{18}F]-DOPA) positron emission tomography (PET) to identify focal pancreatic lesions in 14 CHI patients, 11 of which carried mutations in the *ABCC8* gene (age 1–42 months). To reduce bias in PET image interpretation, quantitative means for evaluation of pancreatic [^{18}F]-DOPA uptake were established. Five patients had a visually apparent focal accumulation of [^{18}F]-DOPA and standardized uptake value (SUV) >50% higher (mean 1.8-fold) than the maximum SUV of the unaffected part of the pancreas. When these patients were operated on, a focus of 4–5 × 5–8 mm matching with the PET scan was found, and all were normoglycemic after resection of the focus. The remaining nine patients had diffuse accumulation of [^{18}F]-DOPA in the pancreas (SUV ratio <1.5). Diffuse histology was verified in four of these, and pancreatic catheterization was consistent with diffuse pathology in four cases. In conclusion, [^{18}F]-DOPA PET is a promising noninvasive method for the identification and localization of the focal form of CHI. *Diabetes* 55:13–18, 2006

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[^{18}F]-DOPA, fluorine-18 L-3,4-dihydroxyphenylalanine; CHI, congenital hyperinsulinism of infancy; L-DOPA, L-3,4-dihydroxyphenylalanine; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PACS, pancreatic arterial calcium stimulation; PET, positron emission tomography; PVS, pancreatic venous sampling; SUV, standardized uptake value.

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Congenital hyperinsulinism of infancy (CHI) is a severe disease that carries a high risk of neurological complications secondary to deep uncontrollable hypoglycemia (1,2). This condition is most commonly caused by mutations in the genes (*ABCC8* and *KCNJ11*) encoding one of the subunits (SUR1 or KIR6.2) for the β-cell ATP-sensitive potassium channel. The mutations result in non- or dysfunctional ATP-sensitive potassium channels, which keep the β-cell membrane constantly depolarized and allow continuous insulin secretion (3,4). The most severe forms of CHI are generally caused by recessive SUR1 (*ABCC8*) mutations, leading to continuous hypersecretion of insulin that responds poorly to drug treatment and may thus require near-total pancreatectomy (5).

The histopathological lesions in the pancreas can be diffuse or focal with distinct molecular basis despite having similar clinical presentation. In the largest clinical series published so far, the focal form has represented 40–70% of all cases (6,7). The focal lesion is characterized by adenomatous islet cell hyperplasia, due to the somatic loss of maternal chromosome 11p15 region within a limited region of the pancreas (8). Endocrine hyperplasia and excessive β-cell proliferation within the focal lesion is due to loss of expression of maternally expressed tumor suppressor genes, $p57^{KIP2}$ and H19, and upregulation of the paternally expressed IGF-2 gene (9,10). The adenomatous hyperplasia alone is not sufficient to cause hypoglycemia, but the patient also has to carry a paternally inherited recessive SUR1 (*ABCC8*) or Kir6.2 (*KCNJ11*) mutation. Due to the maternal loss of heterozygosity, the mutation is able to cause dysregulated insulin secretion (11,12).

Distinction between the two histopathological forms is clinically important since near-total pancreatectomy carries a high risk of iatrogenic diabetes, while patients with focal CHI can be completely cured by a limited resection of the hyperfunctional tissue (13). Up to now, differential diagnosis before surgery has been difficult. Invasive and technically demanding techniques based on pancreatic venous sampling (PVS) or pancreatic arterial calcium stimulation (PACS) have been used (7,14). Although found useful in many cases in some centers, these methods have not been widely accepted or implemented. Thus, there is an obvious need for less invasive methods that could be used more widely. Ideally, the diagnostic method should both distinguish patients with focal versus diffuse pathol-

ogy and localize the focal lesion within the pancreas as precisely as possible to guide surgical resection.

Fluorine-18 L-3,4-dihydroxyphenylalanine ([^{18}F]-DOPA) positron emission tomography (PET) has been extensively used to study brain dopaminergic system in patients with Parkinson's disease. Recently, reports have appeared demonstrating the usefulness of this technique in the detection of pheochromocytomas and gastrointestinal carcinoid tumors (15–17). Because of the neuroendocrine nature of the pancreatic islet cells, we hypothesized that [^{18}F]-DOPA PET could be used for the detection and localization of hyperfunctional islet tissue and that this information could be used for the planning of surgery for the focal forms of CHI (18).

RESEARCH DESIGN AND METHODS

Fourteen CHI patients were studied with [^{18}F]-DOPA PET at the PET Centre in Turku, Finland (Table 1). The focal lesions were confirmed by histology obtained at surgery (n = 5). Pancreatic biopsy was performed in one additional patient, suggesting diffuse pathology. Diffuse forms resistant to medication had near-total pancreatectomy (n = 3), while conservative treatment was chosen for those patients who could be kept normoglycemic on normal feeding by either subcutaneous octreotide (n = 4) or oral diazoxide (n = 2) treatment. The onset of hypoglycemia was neonatal in most cases, but it occurred later, between the ages of 2.5 and 5 months, in three patients. In all the cases, the diagnosis of CHI was based on persistent hypoglycemia with a highly increased glucose demand associated with low blood ketone bodies and free fatty acids together with measurable circulating insulin levels at the time of hypoglycemia. The use of [^{18}F]-DOPA in the diagnostics of hyperinsulinism was approved by the local ethics committees and Finnish National Agency for Medicine.

Catheterization. Treatment with octreotide was stopped for at least 24 h and diazoxide for at least 48 h before the PVS or PACS examinations. Normoglycemia was maintained by glucose infusion, which was carefully adjusted according to frequent blood glucose monitoring. Selective PVS was performed in five patients, either in Helsinki or London, under general anesthesia as described previously (19). PACS was performed in two patients in Helsinki (20,21). This test involved the injection of 0.025 mEq Ca^{2+}/kg body weight into the right hepatic artery (as a negative control), gastroduodenal artery, superior mesenteric artery, and splenic artery. Blood samples for plasma insulin were obtained from the right hepatic vein immediately before and at 30, 60, 90, and 120 s after the intra-arterial calcium infusion.

Magnetic resonance imaging. Because of the limited capacity of PET to yield anatomic information, all patients underwent magnetic resonance imaging (MRI) of the pancreas. The MRI studies were performed under conscious sedation using a 1.5 T high–field-strength scanner. T1-weighted pre- and postgadolinium images, T2-weighted images, and axial PET-reference sequences were obtained. The PET-reference sequence pixel size was adjusted to that of the PET scanner to enable coreading of the anatomic and functional images. PET and MRI image fusion was not performed. Pancreatic MRI could not distinguish between focal and diffuse disease in any case.

[^{18}F]-DOPA PET. The PET studies were performed either under propofol-induced sedation or pentobarbital-induced general anesthesia after a 6-h fast. Octreotide or diazoxide were stopped for at least 24 or 48 h before the examination, respectively. During the PET scan, blood glucose concentration was kept in the low normal range, with a target of 3–3,5 mmol/l. Maximal glucose infusion rates between 6.2 and 26 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} were needed. The patients were placed supine, and before imaging, the bladder was flushed with saline via a catheter to minimize the disturbing effects of the tracer excreted in the urine. The synthesis of 6-[^{18}F]-DOPA followed a previously described electrophilic procedure (22). Each patient received 4 MBq/kg of [^{18}F]-DOPA intravenously as a bolus. The PET examinations were performed using the GE Advance PET scanner (General Electric Medical Systems, Milwaukee, WI) operated in 2D acquisition mode. After 60 min, a whole-body scan was obtained in 4–5 bed positions. Postinjection transmission correction was applied with removable ^{68}Ge/^{68}Ga sources. To obtain images for visual analysis, iterative reconstruction was performed using segmented attenuation correction and ordered subsets' expected maximum likelihood algorithm. The final spatial resolution in reconstructed images was ~6 mm.

PET image analysis. The reconstructed images were evaluated in a 3D display using axial, coronal, and sagittal views to define pancreas, which invariably has a sufficiently high uptake of [^{18}F]-DOPA to distinguish it from the surrounding organs in the upper abdomen (Fig. 1). Variable uptake was seen in gall bladder, biliary duct, and duodenum, which all could be discerned from target tissue uptake by visually correlating PET findings to those on corresponding axial MRI slices (Figs. 2 and 3). Then, regions of interest were outlined on axial slices separately for the pancreatic head, body, and tail to measure uptake of [^{18}F]-DOPA. For comparison of tracer uptake in various parts of the pancreas and the hot spot (if any), standardized uptake values (SUVs) were calculated (23). Any patient with a visually clear [^{18}F] hot spot in the pancreas with maximum uptake (SUV_{max}) measuring ≥1.5 times the maximum pancreatic tracer concentration elsewhere was defined as having focal disease. Reproducibility was assured by making the quantitative analysis by two independent observers (M.S. and H.M.), which resulted in 100% confidence when SUV_{max} was applied. The focal hot spot was transferred and marked to the corresponding axial MRI slice(s) that were given to the surgical team.

Genetic studies. Genetic analysis was performed in all patients to identify mutations causative for CHI. All exons of the SUR1 and KIR6.2 genes were investigated by PCR–single-strand conformation polymorphism as described previously (24). The variant forms of DNA in single-strand conformation polymorphism analysis were analyzed by direct sequencing (Thermo Sequenase Radiolabeled Terminator Cycle Sequencing Kit; USB, Cleveland, OH). The two previously detected founder mutations SUR1-V187D (5) and SUR1-E1506K (24) were screened by direct sequencing in all Finnish patients.

RESULTS

A summary of the clinical details and the results from PET scan, catheterization, and surgery for the 14 patients is presented in Table 1. Based on PVS, focal CHI was suspected in cases 1–3. Preoperative imaging by [^{18}F]-DOPA PET was consistent with a focal form of disease in these three cases, and the suggested focus on PET matched with the location of high-insulin secretion detected by PVS (Tables 1 and 2). Encouraged by these positive findings, two additional patients (9 and 13) underwent successful pancreatic surgery based on focal lesions seen on PET only. All of these five focal cases were confirmed by histology obtained during surgery, and the localization of the hyperinsulinemic focus by the PET scan corresponded to the actual localization. In two patients, the focus was located in the head, in one patient in the neck, and in two patients in the body of the pancreas. All of these patients were normoglycemic, with a normal overnight fasting tolerance, without medications, and on normal feeding after a limited pancreatic resection. The follow-up time is 10–36 months after surgery. An example of a typical focal form of CHI (case no. 1 in Table 1) is shown in Figs. 1 and 2 and another patient classified as having focal CHI (case no. 3) is depicted in Fig. 3.

Table 2 shows quantitative analysis of uptake of [^{18}F]-DOPA in various parts of pancreas. The mean SUVs for [^{18}F]-DOPA of seemingly unaffected parts of pancreatic tissue in 14 patients were as follows: head 2.6 (range 1.7–6.2), body 2.3 (1.6–4.9), and tail 2.4 (1.8–4.8). In all five patients with a visually suspected focus, the SUV_{max} ratio between the affected part of pancreas and the highest value in the seemingly normal pancreas was ≥1.5.

Diffuse pancreatic accumulation of [^{18}F]-DOPA was observed in nine patients and these had a SUV_{max} ratio between 1.0 and 1.4 (Table 2), indicating that tracer uptake was relatively homogenous throughout the pancreas. Diffuse finding on PET was concordant with diffuse insulin secretion at PVS or PACS in four patients (Table 1). Only three patients with suspected diffuse disease underwent surgery (near-total pancreatectomy), and the diffuse type of their disease was confirmed by histological analysis. The remaining six patients could be successfully treated by conservative means, either octreotide (n = 3), diazoxide (n = 2), or their combination (n = 1). In one of these (case no. 7), a pancreatic biopsy with diffuse-type pathol-

TABLE 1
Clinical and genetic characteristics of the patients, together with the findings in PET scan, pancreatic catheterization, surgery, and histology

Patient	Age at diagnosis/PET	*ABCC8* mutation	Response to medication	Glucose need (mg/kg/min)	PET	PVS/PACS	Surgery/histology
1	Neonatal/6 months	V187D (561T>A) (Paternal)	Dzx−, Octr +	12.3	focal/head	focal/head	focal resection/posterior neck PAD: focus 6.8 × 4 mm
2	4 months/13 months	V187D (561T>A) (Paternal)	Dzx−, Octr +	9.5	focal/body	focal/body	focal resection/body PAD: focus 5 × 4 mm
3	Neonatal/6 months	G1469V (4408G>T) (Paternal)	Dzx−, Octr +	12.7	focal/head	focal/head	focal resection/head PAD: focus 8 × 5 mm
4	Neonatal/3.5 years	V187D (561T>A) (Paternal)	Dzx−, Octr +	12.7	diffuse	diffuse*	ND
5	Neonatal/6 months	A113V (338C>T) (Paternal)	Dzx−, Octr +	12.7	diffuse	diffuse	Near-total pancreatectomy PAD: diffuse histology
6	Neonatal/5 years	No mutations	Dzx +	6.5	diffuse	diffuse*	ND
7	3 months/4 years	No mutations	Dzx +	6.5	diffuse	ND	Pancreas biopsy PAD: diffuse histology
8	Neonatal/9 months	G92D (275G>A)	Dzx−, Octr +	10.3	diffuse	ND	Near-total pancreatectomy PAD: diffuse histology
9	Neonatal/1 month	V187D (561T>A) (Paternal)	Dzx−, Octr−	20	focal/head	ND	focal resection/uncinate process PAD: focus 8 × 4 mm
10	Neonatal/2 months	No mutations	Dzx partial, Octr +	6.2	diffuse	ND	ND
11	5 months/13 months	V187D (561T>A) (Paternal)	Dzx−, Octr +	6.4	diffuse	diffuse	ND
12	Neonatal/1.5 months	G474A (de novo)	Dzx−, Octr +	15.9	diffuse	ND	Near-total pancreatectomy PAD diffuse;
13	Neonatal/3 months	C418R (1252T>C) (Maternal)	Dzx−, Octr +	26	focal/body	ND	focal resection/body PAD: focus 10 × 6 mm
14	Neonatal/6 months	A113V (338C>T) (Paternal)	Dzx−, Octr +	13	diffuse	ND	ND

The glucose need refers to the glucose infusion rate that was required to maintain normoglycemia at the time of the PET scan. *PACS instead of PVS. Dzx, diazoxide; ND, not done; Octr, octreotide.

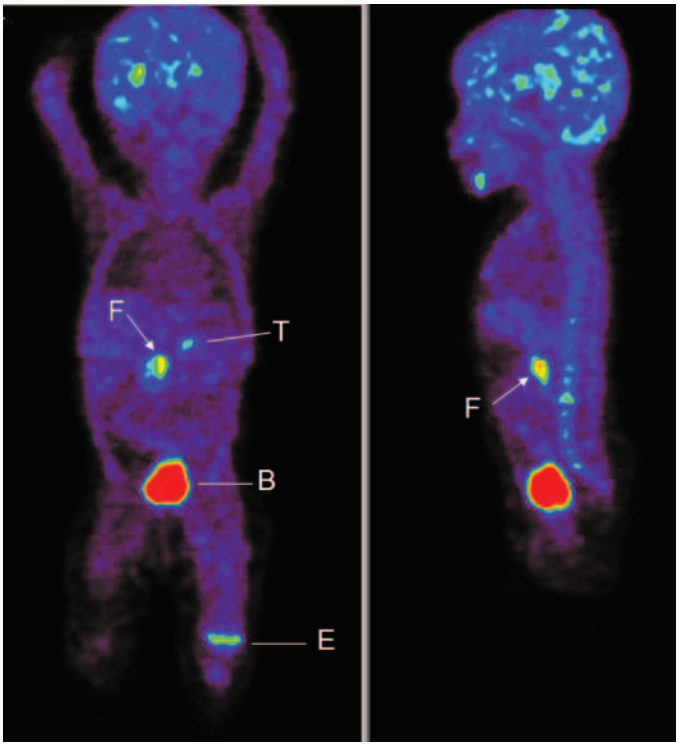

FIG. 1. Whole-body tracer distribution of [^{18}F]-DOPA depicted in coronal and sagittal views of a patient with focal CHI (patient 1). The hyperinsulinemic focus with a maximum tracer SUV of 4.0 in the medial aspect of the pancreatic head (f) is shown with a white arrow. Despite the continuous flushing with saline, the bladder (b) is well visualized. Other areas with positive tracer uptake and indicated with white lines are the pancreatic tail with maximum SUV of 2.6 (t) and the epiphyseal plate (e) of the left distal femur. Note also the moderate uptake in the bone marrow behind the focus seen in the sagittal view.

ogy was obtained. PET scan of one patient with diffuse disease is illustrated (Fig. 4).

Genetic analysis showed that five of the patients were

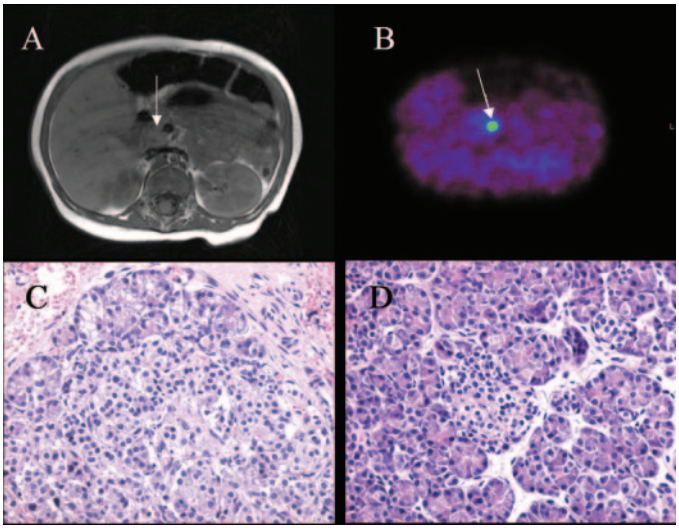

FIG. 2. Representative illustrations of a patient with focal CHI who carries the paternally inherited SUR1-V187D mutation (patient 1, Table 1). MRI shows the pancreas without pathologic findings (*A*), while [^{18}F]-DOPA PET shows a focus of high uptake located in the head of the pancreas (arrow in *B*). A focal lesion (size 7 × 4 mm) was resected from the pancreatic neck (*C*). It is formed by the confluence of apparently normal islets, compressing the remaining exocrine pancreas. The endocrine cells have a large cytoplasm, while in the rest of the pancreas (*D*), the islets appear atrophic.

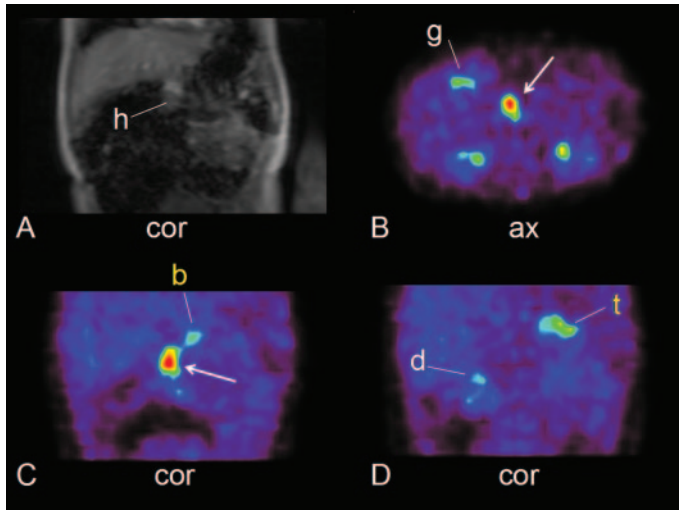

FIG. 3. [^{18}F]-DOPA PET and reference MRI in a 7-month-old infant with a focal form of hyperinsulinism of infancy (patient 3). Coronal MRI (*A*) of the upper abdomen shows pancreatic head (h) and on PET axial (*B*) and coronal (*C*) views a metabolically active focus with a maximum SUV of 6.8 is indicated with white arrow. The maximum SUV of the body of pancreas (b) is 3.1 and that of the tail (t) in another coronal view on PET (*D*) is 3.1, respectively. Of the normal tissues with increased uptake of [^{18}F]-DOPA, both gallbladder (g) and duodenum (d) can be seen.

paternal heterozygotes for the Finnish major founder *ABCC8* mutation V187D (Table 1). In addition, six other mutations of the *ABCC8* gene were found. No *KCNJ11* mutations were found. All of the confirmed focal patients were heterozygous for a SUR1 mutation. As expected, this was paternally inherited in four cases. However, in one patient (no. 13), the only mutation identified (C418R) was inherited from the maternal side. Still, the focal lesion was histologically very typical and its resection was curative.

TABLE 2
Uptake of [^{18}F]FDOPA expressed as maximum standardized uptake value (SUV_{max}) in hyperinsulinemic foci and different parts of pancreas in 14 infants with neonatal hyperinsulinism referred to PET

Patient no.	Location of visible focus	SUV_{max} of pancreas*			Pancreas ratio†
		Tail	Body	Head	
1.	Head	2.6	2.0	4.0	1.5
2.	Body	3.2	6.7	3.6	1.9
3.	Head	3.1	3.1	6.8	2.2
4.	None	4.2	4.2	3.4	1.2
5.	None	2.7	2.4	2.6	1.0
6.	None	3.4	2.6	4.6	1.4
7.	None	5.0	3.0	4.9	1.0
8.	None	4.7	6.7	5.6	1.2
9.	Head	2.2	2.1	**3.4**	1.6
10.	None	6.7	7.5	8.8	1.1
11.	None	3.1	2.7	2.7	1.1
12.	None	3.2	2.4	3.4	1.1
13.	Tail/Body‡	4.5	2.0	2.3	2.0
14.	None	3.8	3.3	4.9	1.3

*SUV obtained from visually appearing focal lesion marked in bold face. †Pancreas ratio is the highest maximum SUV value of the pancreas divided by the next highest maximum SUV value of different and visually unaffected part of the pancreas. ‡The location of lesion was classified as being intermediate between tail and body of pancreas. In SUV_{max} analysis it has been designated as tail lesion to enable calculation of pancreas ratio. The case numbers are the same as in Table 1.

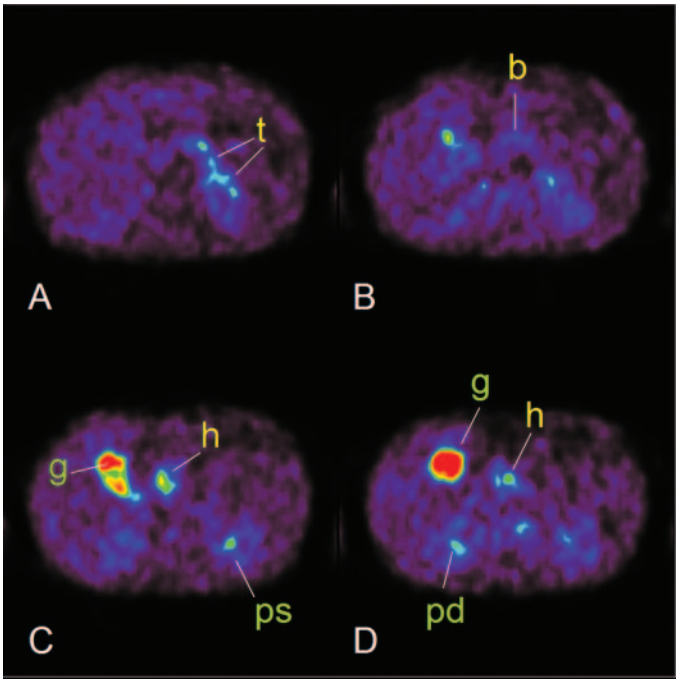

FIG. 4. Axial [^{18}F]-DOPA PET views at four levels (*A-D*) showing pancreas and some other tissues with physiologically increased tracer uptake in a 5-year-old girl (patient 6) presumably having a diffuse form of hyperinsulinism of infancy. In *A*, the pancreatic tail (t) has maximum [^{18}F]-DOPA SUV of 3.4, while that of the body of pancreas (b) in *B* is 2.6 and of the head of pancreas (h) in *C* and *D* is 4.6. The gallbladder (g in *C* and *D*) has much higher uptake of tracer than pancreas in this case, where both kidneys (ps in *C* and pd in *D*) can be visualized as well. This case had the highest SUV_{max} ratio (1.4) among all classified as diffuse. Although a focus in pancreatic head cannot totally be ruled out, the negative PACS result, the absence of *ABCC8* mutation, and the good response to diazoxide treatment left us to withhold from surgery.

This is remarkable because until now, focal hyperinsulinism of infancy has always been associated with a paternal mutation together with maternal loss of heterozygocity. In this case, the $p57^{Kip2}$ gene product, which is normally maternally expressed, was lost within the lesion, and also the mapping of single nucleotide polymorphic markers verified maternal loss of heterozygocity at chromosome 11p (not shown). Thus, the mutation C418R was apparently not expressed within the lesion and is likely not of functional importance.

No mutations were found in three patients, and these were the only ones who could be successfully treated with diazoxide or a combination of diazoxide and octreotide. Heterozygous SUR1 mutations were found also in six of the nine patients classified as diffuse based on PET. Three of these underwent near-total pancreatectomy, and diffuse pathology was confirmed in all of them. The other three patients could be maintained in normoglycemia with low-dose continuous subcutaneous octreotide infusion. In one of these, the medication could be stopped after 3 years' treatment. The patient has been normoglycemic with a normal fasting tolerance since then. It is possible that some of these patients had a focal lesion that was too small to be detected by the PET scan.

DISCUSSION

Our experience from 14 patients indicates that it is possible to identify the focal forms of CHI using the noninvasive [^{18}F]-DOPA PET. We found focal accumulation of [^{18}F]-DOPA in the pancreas of five patients, and a focal lesion was confirmed histologically in each case. All these infants underwent limited pancreatic resection guided by perioperative biopsies, and all of the patients have remained normoglycemic without treatment. Diffuse pathology was confirmed in four of the nine patients showing diffuse pancreatic accumulation of [^{18}F]-DOPA. We can, however, not exclude the possibility that a small focal lesion was missed in the three cases who were carrying a heterozygous *ABCC8* mutation and maintained on medication without surgery. We attest also that tracer uptake in different parts of pancreas may show some physiological variation (see Table 2) and this together with limited resolution may compromise sensitivity to detect focal CHI. We suggest that whenever surgery is planned, it should consider resection of the hottest region of pancreas seen on PET even if the focus is not totally evident in visual and quantitative analysis.

The ability of neuroendocrine tumors (NETs) to accumulate L-3,4-dihydroxyphenylalanine (L-DOPA) led to the original amine precursor uptake and decarboxylation concept, and the later erroneous conclusion that pancreatic islet cells differentiate from neuronal precursors (25). However, islets do take up L-DOPA and convert it to dopamine by DOPA decarboxylase, present in the islet cells (26). Alhström et al. (27) were the first to visualize pancreatic NETs with ^{11}C-labeled DOPA. Of three insulinomas, only one could be imaged with this technique. Recently, Becherer et al. (17) studied 23 patients with advanced NET with [^{18}F]-DOPA PET. Seven patients had originally pancreatic NETs. [^{18}F]-DOPA was sensitive to find all those three cases who had a pancreatic tumor at the time of scanning and was negative on all 20 cases without pancreatic metastasis (specificity 100%). It should be noted that many adult insulinomas consist of relatively poorly differentiated cells with low levels of insulin synthesis and secretion. In contrast, infantile hyperinsulinemic foci contain highly differentiated hyperfunctioning islet cells and are thus fundamentally different from adult insulinomas. Importantly, normal islets adjacent to a focal CHI lesion are in the resting state, unlike the islets adjacent to an insulinoma (10). These observations could explain why focal CHI is more readily identified than insulinomas by a specific metabolic feature, such as L-DOPA uptake.

Based on our very encouraging initial experience we conclude that [^{18}F]-DOPA PET is a promising method both for the identification of focal and diffuse CHI and the localization of the hyperinsulinemic focus. However, the final value of this diagnostic technique can only be estimated when a larger number of patients have been studied in multiple centers. The localization provided by PET seems to be as precise as that obtained by PVS and should be sufficient to guide the surgical resection in most cases. Coregisteration of PET and MRI images assists in distinguishing between focal activities within and outside the pancreas and appears to be necessary for optimal planning of surgery. Most likely, future studies will be performed with hybrid PET/computed tomography scanners, which enable correlation of anatomic and functional information within one imaging session and under a single anesthetic procedure. Considering the invasiveness and technical difficulty of the other diagnostic alternatives, [^{18}F]-DOPA PET should be considered as a primary differential diagnostic tool in infantile hyperinsulinemic hypoglycemia. With improved sensitivity, this method might also provide

new possibilities for the functional imaging of the endocrine pancreas in other conditions.

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