Diagnosis and Localization of Focal Congenital Hyperinsulinism by ^{18}F-Fluorodopa PET Scan

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Objectives To assess the accuracy of ^{18}F-fluoro-L-dihydroxyphenylalanine ([^{18}F]-DOPA) PET scans to diagnose focal versus diffuse disease and to localize focal lesions in infants with congenital hyperinsulinism.

Study design Twenty-four infants with hyperinsulinism unresponsive to medical therapy were studied. Patients were injected intravenously with [^{18}F]-DOPA, and PET scans were obtained for 1 hour. Images were coregistered with abdominal CT scans.

Results The diagnosis of focal or diffuse hyperinsulinism was correct in 23 of the 24 cases (96%) and equivocal in 1 case. [^{18}F]-DOPA PET identified focal areas of high uptake of radiopharmaceutical in 11 patients. Pathology results confirmed that all 11 had focal adenomatosis, and the locations of these lesions matched the areas of increased [^{18}F]-DOPA uptake on the PET scans in all of the cases.

Conclusions [^{18}F]-DOPA PET scans were 96% accurate in diagnosing focal or diffuse disease and 100% accurate in localizing the focal lesion. These results suggest that [^{18}F]-DOPA PET imaging should be considered in all infants with congenital hyperinsulinism who need to have pancreatectomy. *(J Pediatr 2007;150:140-5)*

Congenital hyperinsulinism, the most common cause of persistent hypoglycemia in infants and children, is most often associated with recessive mutations of the β-cell ATP-sensitive potassium (K_{ATP}) channel. The channel is encoded by two adjacent genes on chromosome 11p15.1, *SUR1* and *Kir6.2*. In cases of diffuse disease, patients have mutations of both alleles encoding the K_{ATP} channel resulting in dysregulation of insulin secretion from all β-cells.[1,2] Recessive K_{ATP} mutations may also cause focal hyperinsulinism in which there is an area of β-cell adenomatosis caused by loss of heterozygosity for the maternal 11p region and expression of a paternally derived K_{ATP} channel mutation.[3,4] Surgical intervention is often necessary to control hypoglycemia in both forms of K_{ATP} hyperinsulinism but is only curative in the cases of focal disease.

Surgical treatment of infants with congenital hyperinsulinism depends on being able to distinguish between focal and diffuse disease and to locate focal lesions. Functional tests of insulin responses to secretagogues before surgery are unable to reliably distinguish focal versus diffuse disease, in part because some disease-causing mutations of the K_{ATP} channel retain partial function.[5-7] Focal lesions are rarely identifiable at surgery and cannot be detected by using conventional imaging techniques such as computed tomography, magnetic resonance imaging, transabdominal or intraoperative ultrasound, or by the use of radiolabeled octreotide scans.[8] Interventional radiologic techniques such as selective pancreatic arterial calcium stimulation with hepatic vein insulin sampling (ASVS) and transhepatic portal venous insulin sampling (THPVS) are invasive, technically difficult, and are also not reliable in either diagnosing or localizing focal lesions.[3,7]

Neuroendocrine cells have an affinity for taking up and decarboxylating amino acid precursors.[9,10] Consequently, amino acid precursors such as L-dihydroxyphenylalanine (L-DOPA) may be taken up by these cells and become decarboxylated to dopamine through the action of aromatic amino acid decarboxylase (AADC).[11-13] Neuroendocrine

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ASVS	Selective pancreatic arterial calcium stimulation with hepatic vein insulin sampling	[^{18}F]-DOPA	^{18}F-fluoro-L-dihydroxyphenylalanine
		THPVS	Transhepatic portal venous insulin sampling

tumors such as carcinoids and pheochromocytomas have been successfully localized with the use of ^{18}F-fluoro-L-dihydroxyphenylalanine ([^{18}F]-DOPA) PET.[14,15]

A preliminary report from Otonkoski et al[16] suggested that [^{18}F]-DOPA PET scans could image focal lesions in congenital hyperinsulinism. Two small series of cases supporting this suggestion have been recently reported.[17-19] The current study was undertaken to test prospectively both the accuracy of [^{18}F]-DOPA PET scans in diagnosing focal disease and its ability to localize focal lesions in children with congenital hyperinsulinism. The study was designed to have a sample size of 50 cases, of which half were expected to be focal. This preliminary report provides analysis of the first 24 cases and suggests that the accuracy of [^{18}F]-DOPA PET scanning is better than anticipated for both diagnosis and localization of focal hyperinsulinism.

METHODS

Subjects

All of the patients included in this study were referred to the Hyperinsulinism Center at the Children's Hospital of Philadelphia between December 2004 and November 2005 for surgical treatment of medically uncontrollable hyperinsulinism. Patients not requiring surgery and patients who had previous pancreatectomies were excluded. The diagnosis of hyperinsulinism was based on previously described criteria: fasting hypoglycemia accompanied by inadequate suppression of plasma insulin, inappropriately low plasma free fatty acid and plasma β-hydroxybutyrate concentrations, and an inappropriate glycemic response to glucagon injection.[20,21] Two of the infants underwent ASVS testing before surgery. Mutation analysis of K_{ATP} genes was performed by sequencing coding exons and flanking intronic regions of genomic DNA from peripheral blood leukocytes (Athena Diagnostics, Worcester, MA). In all cases, results of mutation analyses were not available before surgery. Loss of heterozygosity in focal lesions was identified by haplotype analysis through the use of microsatellite markers and by absence of p57^{KIP2} immunostaining in paraffin-embedded surgical specimens.[3,4,22,23]

Surgical Technique and Intraoperative Frozen Section Evaluation

All of the infants underwent pancreatectomy between 2 weeks and 18 months of age. PET scans were performed at least 12 hours before surgery (6 half-lives). The results of the interpretation of the PET scan were made available to the surgeon to help in the identification of potential focal lesions. During surgery, biopsy specimens from three areas of the pancreas were obtained and examined for β-cells with enlarged nuclei suggestive of diffuse disease. The absence of nuclear enlargement indicated the presence of a focal lesion. Findings from the PET scan were compared with the findings at pathology, based on permanent sections, as described by others.[24-25] The determination of focal versus diffuse disease was made on the permanent histologic sections by two pathologists who were masked to the results of the PET scan.

Imaging Technique

[^{18}F]-DOPA PET scans were performed at the University of Pennsylvania PET Imaging Facility. The [^{18}F]-DOPA was administered under an Investigational New Drug (#48923) reviewed by the Radiation Safety Committee, Institutional Committees, and the Food and Drug Administration. The Investigational New Drug was modified to allow inclusion of children, and the Food and Drug Administration dosimetry studies are part of that application. The isotope was manufactured by the Cyclotron Facility at the University of Pennsylvania on the day of the test, using the procedure previously published.[26] Typical yields were 10 to 15 mCi for a 500 micro-amp-minute irradiation. Specific activity of the compound is approximately 500 to 1000 Ci/mol at end of synthesis. Patient injection occurred about 45 minutes after completion of the synthesis. Medications that could potentially interfere with pancreatic β-cell function, such as diazoxide, octreotide, and glucagon, were discontinued 5 days, 2 days, and 12 hours, respectively, before the procedure. All patients received intravenous dextrose infusion for control of hypoglycemia and to enhance elimination of isotope from the kidneys. Plasma glucose was monitored before and every 60 minutes during the procedure. Rates of intravenous glucose infusion were adjusted as needed to maintain plasma glucose levels greater than 70 mg/dL. In one case, the patient was catheterized to facilitate bladder emptying. For obtaining PET images, patients were intubated and sedated with general anesthesia. Patients were injected intravenously with 3 to 6 MBq/kg (0.08 to 0.16 mCi/kg) of [^{18}F]-DOPA, which is approximately one-tenth of the total adult dose. After injection, five or six consecutive 10-minute-long scans were performed. The images were acquired through the use of a dedicated brain PET camera based on Anger-logic gadolinium oxyorthosilicate (GSO) detectors, designed and built by the Physics and Instrumentation Group at the University of Pennsylvania.[27] This instrument has both axial and transverse fields of view of 25 cm and is therefore suited for imaging the whole body in infants. An abdominal CT was obtained separately to define the anatomy of the pancreas and adjacent tissue before surgery. The CT image was coregistered with the PET scan to assist in defining the location of focal lesions by using standard software that is available for this purpose.

The study protocol was approved by the Food and Drug Administration and the institutional review boards of the Children's Hospital of Philadelphia and the University of Pennsylvania. Written informed consent was obtained from the parents of the patients.

Image Interpretation

The image set for each patient was visually interpreted by one of the investigators at the completion of the examination. Images were reviewed in all three planes as well as

Table I. Clinical features of infants with hyperinsulinism studied with [^{18}F]-DOPA PET scan before surgery [median (range)]

Characteristic	Diffuse disease	Focal disease
No.	12	12
Sex, M/F	6/6	8/4
Large for gestational age	83%	83%
Age at first symptoms (d)	1 (1-4)	1 (1-90)
Age at PET (wk)	5 (2-72)	7 (2-56)
ASVS performed	0	2

maximum intensity projection views, and the presence and the pattern of uptake in the pancreas were taken into consideration in generating final reports for these scans. The image examination was considered positive for focal disease when the uptake of the radiotracer in part of the pancreas was qualitatively higher when compared with the uptake in the remaining pancreatic tissue and other surrounding background organs. In contrast, when the entire pancreas was visualized with nearly uniform [^{18}F]-DOPA uptake, the examination was considered to represent diffuse disease.

Statistical Analysis

Based on previous reports on ASVS and THPVS from Paris and Philadelphia, we assumed that 50% of surgical cases would have focal disease and that at least 70% of focal lesions would be correctly localized by [^{18}F]-DOPA PET test.[16,19] Sample size estimates based on these assumptions indicated that 52 total cases (26 focal cases) would provide an estimate of test accuracy between 52% and 88% (95% confidence interval, CI). The efficient-score method was used to calculate 95% CIs for proportions.[28]

RESULTS

Table I summarizes the clinical features of the 24 infants with medically unresponsive hyperinsulinism who were studied with [^{18}F]-DOPA PET scans before surgery. Most of the infants in both groups were large for gestational age, presented with hypoglycemia at birth, and were referred for pancreatectomy within a few months after birth.

ASVS testing was done in patient 13 and patient 15 before surgery. In both, ASVS showed a step-up in insulin release after calcium infusion in the gastroduodenal artery, suggesting a focal lesion in the head of the pancreas. Although the ASVS test was correct in diagnosing focal disease in both cases, it was correct in localizing the lesion only in patient 13 (Table II).

After intravenous injection of [^{18}F]-DOPA, the uptake of isotope into pancreas and other tissues, such as liver, was rapid and then remained essentially constant from 10 to 60 minutes. There was also uptake early in the kidneys and bladder that decreased with time as radiopharmaceutical was excreted in the urine. Drainage of urine through a Foley catheter helped decrease the intensity of uptake in the bladder region in one patient. No patients became hypoglycemic during the PET scan.

Figures 1 and 2 show illustrative PET scans of cases with diffuse and focal hyperinsulinism. Figure 1A shows the maximum intensity projection image from a diffuse case (patient 4) with uniform [^{18}F]-DOPA uptake throughout the pancreas. The intensity of uptake in the pancreas was greater than in the liver and surrounding tissue but less than in the renal calyces. Figure 1 (B through D) shows the same case with the abdominal CT scan and PET scan separate and coregistered, which confirms that the diffuse uptake of [^{18}F]-DOPA was in the pancreas.

Figure 2 shows a focal case (patient 23) in which there was a discrete area of [^{18}F]-DOPA uptake in the head of the pancreas. There was also uptake in the neighboring normal pancreatic tissue, but it was less intense than in the head of the pancreas (Figure 2A). Coregistration of the PET and CT scans from patient 23 (Figure 2, B through D) demonstrates that the location of the focal uptake was in the head of the pancreas.

Diffuse uptake of [^{18}F]-DOPA was observed throughout the pancreas of patient 17, with areas of intense uptake in the head, body, and tail of the pancreas. This scan was interpreted as being either consistent with diffuse disease or, possibly, an extensive focal lesion. The latter possibility was confirmed at surgery, where an extensive area of islet adenomatosis occupied 80% to 90% of the pancreas and extended throughout the body, tail, and most of the head of the gland.

Table II summarizes the results of the PET scans and the histologic diagnoses in the 24 cases studied. In all of the 12 diffuse cases, the preoperative interpretation of the PET scan was the same as the histologic diagnosis of diffuse disease. In 11 of the 12 cases of focal disease, focal uptake of isotope on PET correctly diagnosed the presence of focal disease. As noted above, the one case with an extensive focal lesion was suggested but not definitively diagnosed as a focal lesion by PET. However, in all of the 12 cases of focal disease, including the case with focal adenomatosis over 80% to 90% of the gland, the PET scan correctly indicated the location of the lesions. There were no side effects observed that could be attributed to the radiopharmaceutical.

As shown in Table II, mutation analysis of the two K_{ATP} genes identified two mutations consistent with diffuse disease in 7 of the 11 diffuse cases in whom mutation analysis was completed. In two other diffuse cases, only one of the expected two mutations could be identified. In two of the diffuse cases, no mutation could be found in either maternal or paternal allele. Among the 12 focal cases, mutation analysis showed a paternal-only mutation in 11 cases. Immunohistochemical staining for p57^{KIP2} and haplotype analysis demonstrated loss of heterozygosity for the maternal 11p region in all of the 12 focal cases.

In addition to the 24 cases who fit the study inclusion criteria, [^{18}F]-DOPA PET scans were done in 3 additional patients. In one of these patients who did not fit inclusion criteria, medical treatment with octreotide was sufficiently

Table II. Results of preoperative [^{18}F]-DOPA PET scans in 24 infants with congenital hyperinsulinism

Patient No.	[^{18}F]-DOPA PET diagnosis	Histologic diagnosis	*Kir6.2* or *SUR1* mutations		LOH by haplotyping and immunostaining
			Paternal	Maternal	
Diffuse disease					
1	Diffuse	Diffuse	none	none	
2	Diffuse	Diffuse	g3992-9a	G173R	
3	Diffuse	Diffuse	none	none	
4	Diffuse	Diffuse	31aa insertion	g1630+1t	
5	Diffuse	Diffuse	del20aa	none	
6	Diffuse	Diffuse	R837X	15aa insertion	
7	Diffuse	Diffuse	Q219X	none	
8	Diffuse	Diffuse	R620C	E501L	
9	Diffuse	Diffuse	Q444H	Q444H	
10	Diffuse	Diffuse	ND	ND	
11	Diffuse	Diffuse	g3992-9a	1388delF	
12	Diffuse	Diffuse	R999X	R999X	
Focal disease					
13	Head	Head and neck	E282K	none	LOH
14	Head	Head	D310V	none	LOH
15	Body	Body	g1630+1t	none	LOH
16	Head	Head	g2041−21a	none	LOH
17	Extensive lesion	Extensive lesion	R1461C	none	LOH
18	Tail	Tail	D1472N	none	LOH
19	Tail	Tail	E490X	none	LOH
20	Head	Head	g3992−9a	none	LOH
21	Tail	Tail	G954X	none	LOH
22	Head	Neck	ND	ND	LOH
23	Head	Head	del6aa	none	LOH
24	Head	Head	t1176+2c	none	LOH

ND, not done; *LOH*, loss of heterozygosity.

effective so that surgery was not considered mandatory. However, a focal lesion was suspected on the basis of the presence of a single paternal K_{ATP} mutation. The PET scan showed focal uptake in the head of the pancreas suggesting a focal lesion; surgery was elected that revealed a focal lesion, which was excised. In a second patient, two prior pancreatectomies at another institution had removed 98% of the pancreas but failed to improve hypoglycemia. A focal lesion was detected in the head of the pancreas but not completely excised in the second surgery. [^{18}F]-DOPA PET scan showed areas of focal uptake not only in the remaining head of the gland but also in four ectopic extrapancreatic areas. At surgery, the residual focal lesion in the head of the pancreas was resected, as were four ectopic focal adenomatosis lesions in the wall of the jejunum. (Details of this case will be reported separately.) In the third case, the parents declined surgical treatment on the basis of the interpretation of the [^{18}F]-DOPA PET scan as diffuse disease. Although these three patients could not be included in our study of the [^{18}F]-DOPA PET scan accuracy, the test did correctly localize the focal lesions in two of the three patients.

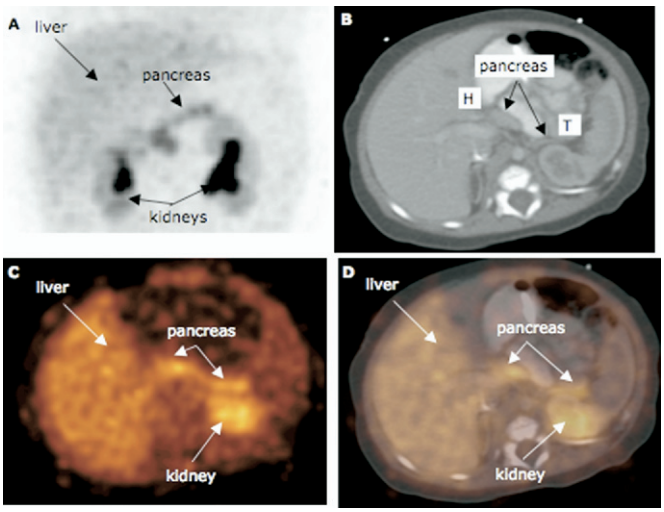

Figure 1. [^{18}F]-DOPA PET of patient 4 with diffuse disease. **A,** Diffuse uptake of [^{18}F]-DOPA is visualized throughout the pancreas on this depth-weighted maximum intensity projection sagittal image. Intensity is greater than that observed in the liver and surrounding tissue. Also note physiologic distribution in the kidneys. Transverse views show **B,** normal pancreatic tissue on abdominal CT; **C,** diffuse uptake of [^{18}F]-DOPA in pancreas; and **D,** confirmation of pancreatic uptake of [^{18}F]-DOPA with coregistration. *H* indicates head of pancreas; *T*, tail of pancreas.

DISCUSSION

These preliminary results suggest that [^{18}F]-DOPA PET is accurate in both the diagnosis of focal or diffuse

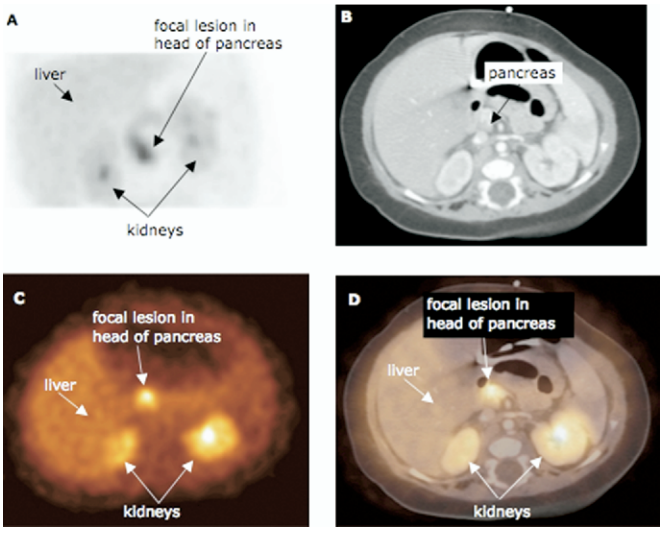

Figure 2. [^{18}F]-DOPA PET of patient 23 with focal disease. **A,** Discrete area of increased [^{18}F]-DOPA uptake is visualized in the head of the pancreas on this depth-weighted maximum intensity projection image. The intensity of this area is greater than that observed in the liver and neighboring normal pancreatic tissue. Transverse views show **B,** normal pancreatic tissue on abdominal CT; **C,** focal uptake of [^{18}F]-DOPA in pancreatic head; and **D,** confirmation of [^{18}F]-DOPA uptake in the pancreatic head with coregistration.

hyperinsulinism and the localization of the focal lesion. Diagnosis was correct in 23 of 24 cases and equivocal in 1 case (96%; CI, 77% to 98%). Of the 12 focal lesions, [^{18}F]-DOPA PET localized the focal lesion in all of the cases, providing a 95% CI between 70% and 100%.

In assessing the accuracy of this new technique, it is important to differentiate diagnosis of the form of hyperinsulinism from localization of the focal lesion. There may be clinical situations in which surgery would not be considered unless the patient has focal disease. In such cases, it is crucial to know the accuracy of the PET scan in diagnosing focal hyperinsulinism so that patients with focal disease can undergo curative surgery. In the current series, the sensitivity of [^{18}F]-DOPA PET in diagnosing focal disease was 92% and the specificity was 100%. The positive predictive value of [^{18}F]-DOPA in diagnosing focal disease was 100% (11/11) and the negative predictive value was 92% (12/13). Localization is a separate issue because successful surgery depends on finding and removing the focal lesion. For example, if [^{18}F]-DOPA PET definitively identifies the lesion in the head of the pancreas, the surgeon can perform a proximal pancreatectomy with Roux-en-Y and preserve the tail of the pancreas.

The accuracy of [^{18}F]-DOPA PET in our series is consistent with data reported in two smaller series of cases. Otonkoski and colleagues[17] reported that [^{18}F]-DOPA PET was able to correctly diagnose focal versus diffuse disease in nine patients and accurately localized the lesion in all of their five focal cases. Ribeiro et al[19] showed that in nine patients who had surgical treatment, [^{18}F]-DOPA PET accurately diagnosed focal versus diffuse disease and correctly localized the lesion in all five focal cases. Both series included cases in which the [^{18}F]-DOPA PET scan suggested diffuse disease, but surgery to confirm the diagnosis was not done. This is in contrast to our study, in which histopathologic diagnosis was available for all of the 24 cases.

The current data suggest that [^{18}F]-DOPA PET has the potential to be more accurate than ASVS or THPVS in diagnosing focal versus diffuse disease and localizing the focal lesion. ASVS correctly diagnosed diffuse disease in only 4 of 13 cases and localized the focal lesion in only 73% of 33 cases.[7] Of 45 cases of focal disease, THPVS localized the focal lesion correctly in only 75%.[3] In addition, even though PET scans require general anesthesia and a minimal dose of radioactivity, the method is much less invasive than ASVS or THPVS and does not require exposure to hypoglycemia or large volumes of blood.

The results of mutation analysis and testing of focal lesions for loss of heterozygosity in Table II are consistent with the concept that diffuse disease is caused by recessive mutations of the K_{ATP} channel and that focal disease is caused by expression of a paternally derived channel mutation. Evidence for loss of heterozygosity for 11p was demonstrated in all of the focal cases. Mutations in *Kir6.2* or *SUR1* genes were found in both focal and diffuse cases. However, as has been noted in previous series, sequencing of coding regions of peripheral blood genomic DNA failed to uncover all of the expected mutations.[4,7] Mutations could have been present but escaped detection if, for example, they were in regions of DNA not sequenced. Because of the possibility of undetected mutations, DNA sequencing can be informative for diagnosing diffuse disease (mutant maternal allele) but not focal disease.

On the basis of the preliminary results of our study, the [^{18}F]-DOPA PET scan was 96% accurate (CI, 70% to 100%) in diagnosis of focal hyperinsulinism and 100% accurate in localizing the focal lesion. When combined with data from the two other recent reports, the overall accuracy of PET scans has been 100% in localizing focal lesions (21/21; CI, 81% to 100%). These encouraging results suggest that [^{18}F]-DOPA PET imaging should be strongly considered in all infants with congenital hyperinsulinism who fail medical therapy and need to have pancreatectomy.

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