[18]F-6-Fluoro-L-Dopa PET/CT Imaging of Congenital Hyperinsulinism

Lisa J. States[1,2], J. Christopher Davis[1,2], Steven M. Hamel[1], Susan A. Becker[1], and Hongming Zhuang[1,2]

[1]Radiology Department, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Congenital hyperinsulinism is characterized by persistent hypoglycemia due to inappropriate excess secretion of insulin resulting in hyperinsulinemic hypoglycemia. The clinical course varies from mild to severe, with a significant risk for brain damage. Imaging plays a valuable role in the care of infants and children with severe hypoglycemia unresponsive to medical therapy. ^{18}F-6-fluoro-L-dopa PET/CT is the method of choice for the detection and localization of a focal lesion of hyperinsulinism. Surgical resection of a focal lesion can lead to a cure with limited pancreatectomy. This article reviews the role of ^{18}F-6-fluoro-L-dopa PET/CT in the management of this vulnerable population.

Key Words: ^{18}F-FDOPA; hyperinsulinism; congenital hyperinsulinism

Congenital hyperinsulinism (HI) is a rare, life-threatening disease with heterogeneity in clinical presentation, genetic mutations, and histopathology. The estimated frequency of the disease varies by population, with an estimate of 1 in 50,000 live births leading to an estimated incidence of 80 per year in the United States (1). In consanguineous populations, the frequency is as high as 1 in 2,500 (2). Evaluation of hypoglycemia by an experienced endocrinologist is essential for the identification of children who may have a focal lesion that can be cured surgically with limited partial pancreatectomy. Clinical subgroups can be divided into transient perinatal stress, monogenic HI, and syndromic HI. Once transient HI is excluded, the evaluation of the latter subcategories should focus on clinical evaluation and genetic analysis. The main histologic entities found in HI include focal adenomatous islet cell hyperplasia and diffuse β-cell nucleomegaly (3,4). Atypical lesions are found in a small subset of patients.

Genetic analysis has emerged as a valuable tool for the selection of patients who have severe hypoglycemia unresponsive to therapy and who can benefit from imaging with ^{18}F-6-fluoro-L-dopa (^{18}F-FDOPA). A genetic mutation is found in approximately 50% of cases of HI, with defects in the encoding genes of the B-cell adenosine triphosphate–sensitive potassium (KATP) channel to be most common in both focal and diffuse diseases (5). The KATP channel is composed of 4 sulfonylurea receptor 1 protein subunits encoded by the gene ABCC8 and 4 inward-rectifier potassium channel protein subunits encoded by the gene KCNJ11. The absence of normal KATP function resulting in unregulated insulin release can be identified by showing a lack of or a poor response to diazoxide, a KATP channel agonist and the first-line medical therapy for HI in infants (Fig. 1). Both KATP channel genes are localized on chromosome 11p15.1. A single recessive mutation of either gene predicts focal HI with a sensitivity of 97% and a specificity of 91%. Confirmation of paternal inheritance increases the specificity to 93% (6). The proposed mechanism for the loss of heterozygosity is a 2-hit mechanism with paternal mutation in all tissues followed by a somatic loss of maternal 11p15, including the KATP genes and growth regulatory genes. The result is uncontrolled islet cell proliferation forming a focal lesion (7,8).

PATIENT SELECTION

Guidelines for the management of congenital HI include ^{18}F-FDOPA PET in a select group of patients. Once the diagnosis of HI is made, resistance to or the inability to tolerate diazoxide because of side effects is used to identify patients who can benefit from ^{18}F-FDOPA imaging (9,10). The side effects of diazoxide include water and sodium retention, congestive heart failure, nausea, vomiting, and poor appetite (10). Genetic testing may predict the presence of a focal lesion, which can be further evaluated with ^{18}F-FDOPA PET. The initial HI gene panel test includes evaluation for gene mutations in ABCC8 or KCNJ11, found in both focal and diffuse diseases, and gene mutations in GCK or GLUD 1, encoding the enzyme glucokinase or glutamate dehydrogenase, respectively, each a cause of diffuse disease. The finding of paternally inherited or nonmaternally inherited (if paternal results are not available) ABCC8 or KCNJ11 mutations or no identifiable mutations is an indication for imaging with ^{18}F-FDOPA (Fig. 2). Genetic testing can prevent unnecessary scanning of infants with diffuse disease.

^{18}F-FDOPA MECHANISM AND HISTOPATHOLOGY

Localization of a focal lesion is the most important information that imaging can provide as it guides the surgical approach. ^{18}F-FDOPA PET is more accurate in detecting and localizing a focal lesion and less invasive than arterial calcium stimulation with hepatic vein insulin sampling and transhepatic portal venous insulin sampling—both of which require hypoglycemia during blood sample collection (3,11).

The mechanism of uptake of ^{18}F-FDOPA mirrors the metabolism of L-3,4-dihydroxyphenylalanine (L-DOPA), a large neutral amino acid precursor to neurotransmitters such as dopamine, norepinephrine, and epinephrine. The uptake of L-DOPA is seen in neuroendocrine cells, including pancreatic βη-cells. Once inside cells, L-DOPA is converted to L-dopamine by L-DOPA
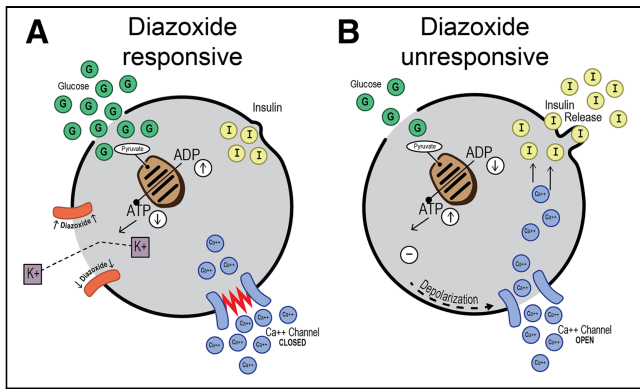
FIGURE 1. (A) Diazoxide-responsive β-cell with normal KATP channel (orange) shows diazoxide keeping channel open and causing hyperpolarization of membrane and inhibition of insulin release. (B) Diazoxide-unresponsive β-cell with failure of KATP channel assembly and tracking to plasma membrane because of ABCC8 or KCNJ11 mutation allows depolarization of membrane with opening of calcium channel causing influx of calcium and unregulated release of insulin. (Courtesy of Serene McLaughlin.)

decarboxylase and is transported into vesicles for storage (12,13). ^{18}F-FDOPA is similarly metabolized and trapped in vesicles, allowing imaging. Uptake in the islets of Langerhans in the pancreas peaks by 5 min after injection and remains fairly constant (14,15). Other sites of activity in the abdomen include the liver, gallbladder, kidneys, and bladder. Uptake may also be seen in pediatric growth plates.

Histopathologic analysis of surgical specimens requires an experienced pathologist for accurate diagnosis. A focal lesion is described as a cluster of abnormal β-cells, referred to as β-cell adenomatosis, and is histologically different from an insulinoma. Lesions consist of a localized area of endocrine islet cell proliferation within otherwise normal pancreatic lobules. The islet cells expand and often distort the involved lobules; however, ducts and exocrine (acinar) cells are observed within lesions. Lesions may have well-circumscribed borders or irregular borders with tentacles of tissue extending into normal tissue. The presence of tentacles can lead to incomplete resection. The histology of diffuse HI is characterized by an increased size of islet cell nuclei (nucleomegaly), measuring at least 3 times the size of neighboring endocrine cell nuclei and 4 times that of acinar cell nuclei, typically seen in islets throughout the pancreas without an overall increase in the volume of endocrine tissue (16–18). Localized islet cell nuclear enlargement is an atypical pathology with features of diffuse HI localized to a portion of the pancreas (6). There is no
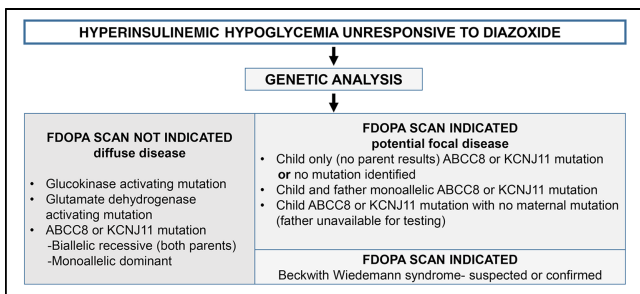
difference in the imaging characteristics of diffuse disease and those of localized islet cell nuclear enlargement (19).

Adzick et al. reported on 500 patients who had HI and who underwent surgery for clinical management (20). Approximately 246 of the 500 patients (49%) had focal disease, with most undergoing 2%–10% pancreatectomy and 97% being "cured." Patients with diffuse disease most often underwent 98% pancreatectomy (20). Atypical disease was found in 37 of the 500 patients (∼7%) who underwent pancreatectomy and included 16 with localized islet cell nuclear enlargement and 21 with Beckwith-Wiedemann Syndrome (BWS) (20). Histopathology in BWS reveals pancreatic endocrine hyperplasia. ^{18}F-FDOPA PET/CT findings may reveal pancreatic enlargement and uptake suggestive of a large lesion (21). Genetic analysis typically reveals a mosaic paternal uniparental isodisomy for chromosome 11p (UDP11p). Most patients do not have KATP channelopathy (22). Ectopic lesions with focal histopathology were seen in 1 of 415 ^{18}F-FDOPA PET scans performed in patients undergoing surgery at the Children's Hospital of Philadelphia.

REVIEW OF LITERATURE

Review of the literature showed growing expertise and great success in the detection and localization of a focal lesion. The studies included in Table 1 were selected if patients underwent surgery and had histopathologic confirmation of focal or diffuse disease. The overall pooled sensitivity and specificity (Fig. 3) were both higher than 90%, with an accuracy of localization ranging from 92% to 100%.

PROTOCOL AND PREPARATION

In 2005, a standardized protocol guideline was created by survey to optimize image quality and minimize radiation (23). A sample protocol used at the Children's Hospital of Philadelphia is depicted in Figure 4. Sedation or anesthesia is required for imaging. Nothing by mouth instructions depend on institution protocols. Withdrawal of glucagon 24 h before a scan has been recommended; however, in our experience at the Children's Hospital of Philadelphia, we have not found it to interfere with uptake in the pancreas. Diazoxide and octreotide are not thought to interfere with uptake and may be continued if necessary. Infusion of glucose-containing fluids is necessary for continued maintenance of safe glucose levels during the scan. To avoid interruption of the glucose infusion, a separate intravenous line is required for tracer injection and iodinated contrast agent injection.

Once the patient is sedated or anesthetized, imaging is performed at a single PET bed over the abdomen. The scout image will confirm appropriate withdrawal of the radiopaque tip of the feeding tube, if present, outside the region of the pancreas. A dose of 4 MBq/kg, suggested by Garg et al. (14), falls within the range of doses used in the publications in Table 1. After the injection of a radiotracer, a noncontrast low-dose CT scan is performed for attenuation correction. PET acquisition starts approximately 10 min after radiotracer injection, with subsequent 10-min sequential acquisitions, for a total of 50 min. Manual injection of contrast agent is used to minimize the risk of extravasation of contrast agent. A contrast-enhanced CT scan of the abdomen performed after the completion of the PET acquisition and fused with the PET data provides a map for surgical planning. A shortened protocol performed with dynamic imaging starting 10 min after injection and using 10-min acquisitions over 30 min can provide similar results. In the United States, all patients are required to

FIGURE 2. Indications for ^{18}F-FDOPA PET/CT using genetic analysis.

TABLE 1
Publications with Surgical Histologic Confirmation of PET Results

| Study | No. of patients | | | No. of atypical cases | Accuracy of localization (%) |
	Undergoing surgery	With focal PET/histology results	With diffuse PET/histology results		
Otonkoski et al. (25) (2006; Finland)	9	5/5	4/4		100
Ribeiro et al. (32) (2007; France)	24	15/15	8/9	3 atypical	92
Hardy et al. (19) (2007; United States)	50	18/24	26/26	1 large focal; 2 localized islet nuclear enlargement	100
Barthlen et al. (33) (2008; Germany)	11	9/9	1/2	1 atypical	100
Masue et al. (26) (2011; Japan)	12	6/9	3/3	3 large focal	33
Zani et al. (49) (2011; United Kingdom)	19	14/14	5/5	1 large focal	79
Laje et al. (28) (2013; United States)	105	45/53	50/52		100
Meintjes et al. (15) (2013; United Kingdom)	8	5/5	3/3		100
Christiansen et al. (35) (2018; Denmark)	34	22/22	12/12	1 atypical; 1 normal; 1 ectopic	91
Gubaeva et al. (50) (2019; Russia)	25	14/14	11/11	1 giant	100
Ni et al. (51) (2019; China)	14	12/12	2/2	Atypical	100
Total	311	165/182 (91%)	125/129 (97%)		
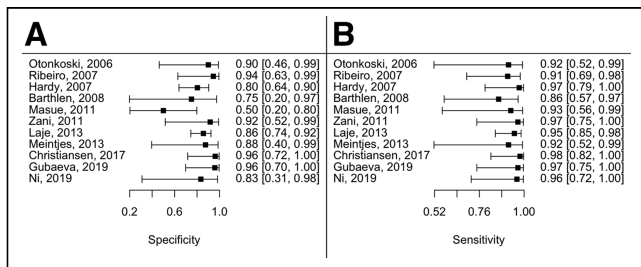
FIGURE 3. Specificity (A) and sensitivity (B) of ^{18}F-FDOPA PET/CT for detection of focal lesions.

sign a written informed consent form before enrollment in an institutional review board–approved protocol under a Food and Drug Administration Investigational New Drug application.

IMAGE INTERPRETATION

Imaging review starts with the attenuation-corrected maximum-intensity projection (MIP) of the entire 50 min of data followed by viewing of the sequentially acquired 10-min MIPs. The 50-min summed MIP is used for image fusion with both noncontrast images and contrast-enhanced images. The lesion is often best detected on the MIP images compared with the fused images and should be seen on more than one 10-min MIP image. Focal lesions
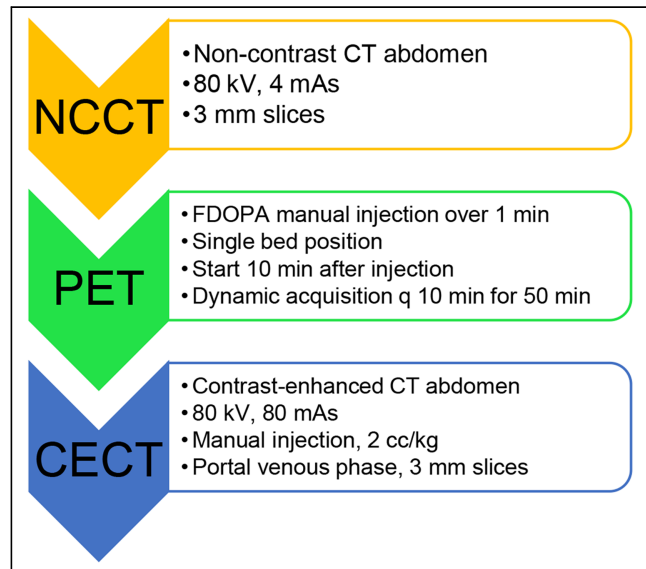

FIGURE 4. Sample imaging protocol. CECT = contrast-enhanced CT; NCCT = noncontrast CT.

typically appear as a focus of increased activity greater than the uptake seen in the normal pancreas (Fig. 5). An abnormal pancreatic contour on CT images can aid in the confirmation of a focal

FIGURE 5. Focal disease. 3-mo-old female with diazoxide-unresponsive HI with ABCC8 mutation. ^{18}F-FDOPA 3-dimensional MIP image at 50 min shows 2 focal lesions, 1 within head (arrow) and other at pancreatic body/tail junction (arrowhead). Lesions were excised with 10% pancreatectomy. Finding 2 lesions is rare occurrence.

lesion (Supplemental Fig. 1) (supplemental materials are available at http://jnm.snmjournals.org). Early images will have the most renal cortical uptake, which can obscure a lesion in the tail. Images performed at 50 min or later may have excretion into the common bile duct, which can be mistaken for a focal lesion in the pancreatic head.

Diffuse disease most often will have homogeneous diffuse uptake (Supplemental Fig. 2). Sometimes, however, uptake can be heterogeneous or appear as multiple lesions (Supplemental Fig. 3) (24). The most common site for a focal lesion is in the head/neck region; this site was seen in 55% of cases by Adzick et al. (20). Difficulty in the detection of a focal lesion can be due to size, shape, and location. The smallest lesion reported as detected was 4 × 5 mm (25). Small lesions in the pancreatic head may be difficult to identify because of the large volume of tissue and background activity in normal tissue. Often, the activity in the pancreatic head is slightly higher than that in the rest of the normal pancreas; this finding is thought to be due to the volume of tissue. Increased activity in the pancreatic head, typically nonfocal, can be seen in the setting of a focal lesion in the body or tail and may be misinterpreted as 2 lesions (Fig. 6). The finding of multiple lesions is rare; however, the possibility should be discussed with the surgeon (Fig. 5). Thin "sheetlike" lesions have been described as missed lesions (26,27).

The location of the lesion is also important. Lesions in the pancreatic tail adjacent to the left kidney can be obscured or overlooked, especially in early images, when the intensity of the tracer in the renal cortex is highest (Supplemental Fig. 4) (28). Ectopic lesions in the small bowel may also be missed if not searched for (29,30). Giant lesions may have heterogeneous activity, with the detection of a focal area but with underestimation of the size and extent of the lesions (31). In addition, a large focal lesion can be confused with diffuse disease (27). Diffuse pancreatic enlargement should raise the possibility of BWS (Fig. 7; Supplemental Fig. 5). Atypical disease was reported in most of the studies in Table 1. Diffuse lesions most often have diffuse homogeneous uptake (Supplemental Fig. 6).

Quantitative analysis has been proposed using an SUV_{mean} ratio (SUV_{mean} of the lesion/SUV_{mean} of normal pancreas) with a cutoff of >1.2 for a focal lesion (25,32,33) or an SUV_{max} ratio (SUV_{max} of lesion/SUV_{max} of normal pancreas) with a cutoff of 1.5 (15,34). Masue et al. reported a high percentage of lesions with irregular uptake or the appearance of multiple lesions (26). In these cases, a comparison of SUV analysis with visual analysis showed an increase in diagnostic accuracy from 50% to 75% (26). Christiansen et al. compared qualitative analysis with the SUV_{max} ratio, using a cutoff SUV_{max} ratio of 1.44 determined by receiver operating characteristic evaluation to predict focal disease (35). Visual criteria performed as well as qualitative criteria (35). Further study

is recommended to determine whether quantitative analysis is helpful in equivocal or atypical cases.

SAFETY

^{18}F-FDOPA has a favorable safety profile. No adverse events have occurred during the administration of ^{18}F-FDOPA synthesized by the University of Pennsylvania cyclotron in 415 scans performed at the Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania. In addition, no adverse events were found in 107 adult patients scanned for neuroendocrine tumor evaluation (36). In a dosimetry study, Garg et al. found a mean effective dose equivalent for ^{18}F-FDOPA of 0.4 ± 0.04 mSv/MBq (14). In comparison, in newborns, the effective dose equivalent for ^{18}F-FDG is 0.43 ± 0.15 mSv/MBq (37). An example given for a PET/CT effective dose using a 25-MBq ^{18}F-FDOPA injection was 13.25 mSv, with ^{18}F-FDOPA contributing 7.55 mSv and low-dose CT for attenuation correction contributing 5.7 mSv. The additional contrast-enhanced CT would include an additional radiation dose. The organs receiving the highest radiation within the field of view are the urinary bladder wall, pancreas, liver, and kidneys. Hydration is essential to minimize the bladder dose. Imaging with PET/MRI can decrease exposure to radiation, but access is currently limited. Alternatively, PET data can be fused with MRI data.

^{18}F-FDOPA has been registered in the European Union since November 2006 (38). A new drug application filed in the United States in 2018 is in review by the Food and Drug Administration (39) and includes the nucleophilic technique as the proposed chemistry, manufacturing and control technique. This synthesis method produces a higher specific activity and a lower mass dose than the traditional electrophilic method and is a simpler procedure (14,40). ^{18}F-FDOPA was approved in October 2019 for use in adults with Parkinson disease (41).

FUTURE CONSIDERATIONS

Carbidopa has been used as a tool to identify insulinoma in adults and has been proposed to decrease normal background activity, enhancing the visualization of a focal lesion (42,43). Christensen
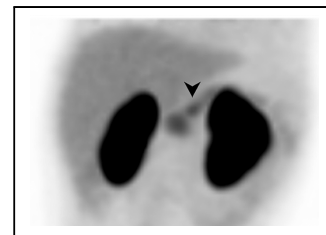

FIGURE 6. Focal lesion in pancreatic body. 3-mo-old female with ABCC8 mutation and paternal mutation. ^{18}F-FDOPA 3-dimensional MIP image shows mild increased activity in pancreatic head and small lesion (arrowhead) in pancreatic body. Focal lesion was found in pancreatic body, abutting vasculature and requiring 50% pancreatectomy.
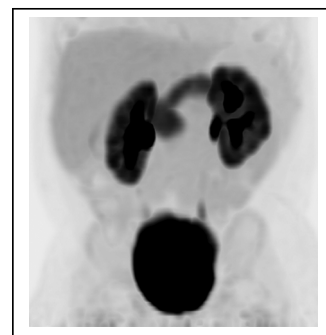

FIGURE 7. BWS. 1-mo-old male with suspected BWS and presenting with HI. ^{18}F-FDOPA 3-dimensional MIP image at 10 min shows uptake within markedly enlarged pancreas, typical of BWS. Increased uptake within enlarged kidneys is also related to patient's syndrome. Patient underwent 95% pancreatectomy.

et al. compared ^{18}F-FDOPA PET/CT with ^{68}Ga-DOTANOC PET/CT and found ^{18}F-FDOPA to be superior (35). The area under the receiver operating characteristic curve was 0.98 (0.93–1) versus 0.71 (0.43–0.95) ($P < 0.03$). Pitfalls of ^{68}Ga-labeled somatostatin receptor imaging include increased uptake in the uncinate process in normal tissue and uptake in splenules, which can be confused with exophytic tail lesions. Intrapancreatic accessory spleen will also have increased activity in somatostatin receptor imaging (44,45) and can cause a false-positive result. Other radiotracers, such as glucagonlike peptide 1 receptor agonists labeled with ^{18}F or ^{68}Ga, have been studied for the evaluation of insulinoma (46–48) in adult populations and are being further explored to determine whether they could be of any value in the management of congenital HI.

CONCLUSION

^{18}F-FDOPA continues to have limited availability in the United States and has not yet been approved by the Food and Drug Administration for the imaging of congenital HI. ^{18}F-FDOPA PET is safe and has been adopted as a standard of care in cases of HI with a suspected focal lesion. The goals are identification and localization. Studies should be performed at sites with a multidisciplinary team with expertise in endocrinology, radiology, surgery, and pathology. A team approach is essential for optimal care of infants and children with HI.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

KEY POINTS

QUESTION: ^{18}F-FODPA PET is the imaging method of choice for the identification and localization of a focal lesion causing congenital HI.

PERTINENT FINDINGS: Hyperinsulinism unresponsive to diazoxide therapy is an indication for ^{18}F-FDOPA PET.

IMPLICATIONS FOR PATIENT CARE: A paternally inherited ABCC8 or KCNJ11 mutation with a loss of heterozygosity is highly predictive of the presence of a focal lesion.

REFERENCES

1. Stanley CA. Hyperinsulinism in infants and children. *Pediatr Clin North Am.* 1997;44:363–374.
2. Bruining GJ. Recent advances in hyperinsulinism and the pathogenesis of diabetes mellitus. *Curr Opin Pediatr.* 1990;2:758–765.
3. de Lonlay-Debeney P, Poggi-Travert F, Fournet JC, et al. Clinical features of 52 neonates with hyperinsulinism. *N Engl J Med.* 1999;340:1169–1175.
4. Han B, Newbould M, Batra G, et al. Enhanced islet cell nucleomegaly defines diffuse congenital hyperinsulinism in infancy but not other forms of the disease. *Am J Clin Pathol.* 2016;145:757–768.
5. Galcheva S, Demirbilek H, Al-Khawaga S, Hussain K. The genetic and molecular mechanisms of congenital hyperinsulinism. *Front Endocrinol (Lausanne).* 2019;10:111.
6. Snider KE, Becker S, Boyajian L, et al. Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. *J Clin Endocrinol Metab.* 2013;98:E355–E363.
7. de Lonlay P, Fournet JC, Rahier J, et al. Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. *J Clin Invest.* 1997;100:802–807.
8. Verkarre V, Fournet JC, de Lonlay P, et al. Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. *J Clin Invest.* 1998;102:1286–1291.
9. Arnoux JB, de Lonlay P, Ribeiro MJ, et al. Congenital hyperinsulinism. *Early Hum Dev.* 2010;86:287–294.
10. Ackermann AM, Palladino AA. Managing congenital hyperinsulinism: improving outcomes with a multidisciplinary approach. *Res Rep Endocr Disord.* 2015;5:103–117.
11. Stanley CA, Thornton PS, Ganguly A, et al. Preoperative evaluation of infants with focal or diffuse congenital hyperinsulinism by intravenous acute insulin response tests and selective pancreatic arterial calcium stimulation. *J Clin Endocrinol Metab.* 2004;89:288–296.
12. Lindström P. Aromatic-L-amino-acid decarboxylase activity in mouse pancreatic islets. *Biochim Biophys Acta.* 1986;884:276–281.
13. Borelli MI, Villar MJ, Orezzoli A, Gagliardino JJ. Presence of DOPA decarboxylase and its localisation in adult rat pancreatic islet cells. *Diabetes Metab.* 1997;23:161–163.
14. Garg PK, Lokitz SJ, Truong L, et al. Pancreatic uptake and radiation dosimetry of 6-[18]fluoro-L-DOPA from PET imaging studies in infants with congenital hyperinsulinism. *PLoS One.* 2017;12:e0186340.
15. Meintjes M, Endozo R, Dickson J, et al. ^{18}F-DOPA PET and enhanced CT imaging for congenital hyperinsulinism: initial UK experience from a technologist's perspective. *Nucl Med Commun.* 2013;34:601–608.
16. Suchi M, MacMullen C, Thornton PS, Ganguly A, Stanley CA, Ruchelli ED. Histopathology of congenital hyperinsulinism: retrospective study with genotype correlations. *Pediatr Dev Pathol.* 2003;6:322–333.
17. Sempoux C, Guiot Y, Dubois D, et al. Pancreatic B-cell proliferation in persistent hyperinsulinemic hypoglycemia of infancy: an immunohistochemical study of 18 cases. *Mod Pathol.* 1998;11:444–449.
18. de Lonlay P, Simon-Carre A, Ribeiro MJ, et al. Congenital hyperinsulinism: pancreatic [18]fluoro-L-dihydroxyphenylalanine (DOPA) positron emission tomography and immunohistochemistry study of DOPA decarboxylase and insulin secretion. *J Clin Endocrinol Metab.* 2006;91:933–940.
19. Hardy OT, Hernandez-Pampaloni M, Saffer JR, et al. Accuracy of [^{18}F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism. *J Clin Endocrinol Metab.* 2007;92:4706–4711.
20. Adzick NS, De Leon DD, States LJ, et al. Surgical treatment of congenital hyperinsulinism: results from 500 pancreatectomies in neonates and children. *J Pediatr Surg.* 2019;54:27–32.
21. Laje P, Palladino AA, Bhatti TR, States LJ, Stanley CA, Adzick NS. Pancreatic surgery in infants with Beckwith-Wiedemann syndrome and hyperinsulinism. *J Pediatr Surg.* 2013;48:2511–2516.
22. Kalish JM, Boodhansingh KE, Bhatti TR, et al. Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome. *J Med Genet.* 2016;53:53–61.
23. Mohnike K, Blankenstein O, Christesen HT, et al. Proposal for a standardized protocol for ^{18}F-DOPA-PET (PET/CT) in congenital hyperinsulinism. *Horm Res.* 2006;66:40–42.
24. States LJ, Saade-Lemus S, De Leon DD. 18-F-L-3,4-dihydroxyphenylalanine PET/computed tomography in the management of congenital hyperinsulinism. *PET Clin.* 2020;15:349–359.
25. Otonkoski T, Nanto-Salonen K, Seppanen M, et al. Noninvasive diagnosis of focal hyperinsulinism of infancy with [^{18}F]-DOPA positron emission tomography. *Diabetes.* 2006;55:13–18.
26. Masue M, Nishibori H, Fukuyama S, et al. Diagnostic accuracy of [^{18}F]-fluoro-L-dihydroxyphenylalanine positron emission tomography scan for persistent congenital hyperinsulinism in Japan. *Clin Endocrinol (Oxf).* 2011;75:342–346.
27. Hardy OT, Hernandez-Pampaloni M, Saffer JR, et al. Diagnosis and localization of focal congenital hyperinsulinism by ^{18}F-fluorodopa PET scan. *J Pediatr.* 2007;150:140–145.

28. Laje P, States LJ, Zhuang H, et al. Accuracy of PET/CT scan in the diagnosis of the focal form of congenital hyperinsulinism. *J Pediatr Surg.* 2013;48:388–393.

29. Peranteau WH, Bathaii SM, Pawel B, et al. Multiple ectopic lesions of focal islet adenomatosis identified by positron emission tomography scan in an infant with congenital hyperinsulinism. *J Pediatr Surg.* 2007;42:188–192.

30. Hussain K, Seppanen M, Nanto-Salonen K, et al. The diagnosis of ectopic focal hyperinsulinism of infancy with [18F]-dopa positron emission tomography. *J Clin Endocrinol Metab.* 2006;91:2839–2842.

31. Kühnen P, Matthae R, Arya V, et al. Occurrence of giant focal forms of congenital hyperinsulinism with incorrect visualization by 18F-DOPA-PET/CT scanning. *Clin Endocrinol (Oxf).* 2014;81:847–854.

32. Ribeiro MJ, Boddaert N, Delzescaux T, et al. Functional imaging of the pancreas: the role of [18F]fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy. *Endocr Dev.* 2007;12:55–66.

33. Barthlen W, Blankenstein O, Mau H, et al. Evaluation of [18F]fluoro-L-DOPA positron emission tomography-computed tomography for surgery in focal congenital hyperinsulinism. *J Clin Endocrinol Metab.* 2008;93:869–875.

34. Capito C, Khen-Dunlop N, Ribeiro MJ, et al. Value of 18F-fluoro-L-dopa PET in the preoperative localization of focal lesions in congenital hyperinsulinism. *Radiology.* 2009;253:216–222.

35. Christiansen CD, Petersen H, Nielsen AL, et al. 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT scans as diagnostic tools in focal congenital hyperinsulinism: a blinded evaluation. *Eur J Nucl Med Mol Imaging.* 2018;45:250–261.

36. Chondrogiannis S, Grassetto G, Marzola MC, et al. 18F-DOPA PET/CT biodistribution consideration in 107 consecutive patients with neuroendocrine tumours. *Nucl Med Commun.* 2012;33:179–184.

37. Ruotsalainen U, Suhonen-Polvi H, Eronen E, et al. Estimated radiation dose to the newborn in FDG-PET studies. *J Nucl Med.* 1996;37:387–393.

38. Chevalme Y-M, Montravers F, Vuillez J-P, et al. FDOPA-(18F): a PET radiopharmaceutical recently registered for diagnostic use in countries of the European Union. *Braz Arch Biol Technol.* 2007;50:77–90.

39. News: FDA reviews NDA for 18F-FDOPA in congenital hyperinsulinims. *J Nucl Med.* 2019;60:7N.

40. Moerlein S, Bognar C, Gaehle G, Oyama R, Schwarz S, Perlmutter J. Validation of a nucleophilic synthesis platform for clinical application of [18F]fluorodopa. *J Nucl Med.* 2017;58(suppl 1):255.

41. Balogova S, Talbot JN, Nataf V, et al. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. *Eur J Nucl Med Mol Imaging.* 2013;40:943–966.

42. Leroy-Freschini B, Amodru V, Addeo P, et al. Early 18F-FDOPA PET/CT imaging after carbidopa premedication as a valuable diagnostic option in patients with insulinoma. *Eur J Nucl Med Mol Imaging.* 2019;46:686–695.

43. Imperiale A, Bahougne T, Goichot B, Bachellier P, Taieb D, Namer IJ. Dynamic 18F-FDOPA PET findings after carbidopa premedication in 2 adult patients with insulinoma-related hyperinsulinemic hypoglycemia. *Clin Nucl Med.* 2015;40: 682–684.

44. Bhure U, Metzger J, Keller FA, et al. Intrapancreatic accessory spleen mimicking neuroendocrine tumor on 68Ga-DOTATATE PET/CT. *Clin Nucl Med.* 2015;40:744–745.

45. Lancellotti F, Sacco L, Cerasari S, et al. Intrapancreatic accessory spleen false positive to 68Ga-Dotatoc: case report and literature review. *World J Surg Oncol.* 2019;17:117.

46. Michalski K, Laubner K, Stoykow C, et al. Detection of insulinomas using dual-time-point 68Ga-DOTA-exendin 4 PET/CT. *Clin Nucl Med.* 2020;45:519–524.

47. Parihar AS, Vadi SK, Kumar R, et al. 68Ga DOTA-exendin PET/CT for detection of insulinoma in a patient with persistent hyperinsulinemic hypoglycemia. *Clin Nucl Med.* 2018;43:e285–e286.

48. Cuthbertson DJ, Banks M, Khoo B, et al. Application of Ga68-DOTA-exendin-4 PET/CT to localize an occult insulinoma. *Clin Endocrinol (Oxf).* 2016;84:789–791.

49. Zani A, Nah SA, Ron O, et al. The predictive value of preoperative fluorine-18-L-3,4-dihydroxyphenylalanine positron emission tomography-computed tomography scans in children with congenital hyperinsulinism of infancy. *J Pediatr Surg.* 2011;46:204–208.

50. Gubaeva DN, Melikyan MA, Ryzhkova DV, et al. Clinical, genetic, and radionuclide characteristics of the focal form of congenital hyperinsulinism [in Russian]. *Probl Endokrinol (Mosk).* 2019;65:319–329.

51. Ni J, Ge J, Zhang M, et al. Genotype and phenotype analysis of a cohort of patients with congenital hyperinsulinism based on DOPA-PET CT scanning. *Eur J Pediatr.* 2019;178:1161–1169.