[¹⁸F]-DOPA Positron Emission Tomography for Preoperative Localization in Congenital Hyperinsulinism

K. Mohnike^a O. Blankenstein^f H. Minn^d W. Mohnike^b F. Fuchtn^c
T. Otonkoski^e

^aDepartment of Pediatrics, Otto-von-Guericke University Magdeburg, Magdeburg; ^bPET Centre Berlin, Berlin, and

^cResearch Centre Rossendorf, Institute for Bioinorganic and Radiopharmaceutical Chemistry, Dresden, Germany;

^dTurku PET Centre and Department of Oncology and Radiotherapy, Turku University Central Hospital, Turku and

^eHospital for Children and Adolescents, University of Helsinki, Helsinki, Finland; ^fDepartment of Experimental Pediatric Endocrinology, Charité-Universitätsmedizin Berlin, Berlin, Germany

Key Words

[¹⁸F]-DOPA-PET/CT • L-DOPA • Congenital hyperinsulinism • Positron emission tomography • Computer tomography

Abstract

In recent years, considerable progress has been made in the biochemical, morphological and molecular genetic differentiation of congenital hyperinsulinism (CHI). Fluorine-18 L-3,4-dihydroxyphenylalanine positron emission tomography (¹⁸F-DOPA-PET) has been introduced for differentiation between focal and diffuse CHI. The ability to take up L-DOPA and convert it into dopamine is correlated with the activity of the aromatic amino acid decarboxylase and increased in the hyperfunctional affected pancreatic area in comparison to normally functioning pancreas. The high sensitivity of this method allows the surgeon to perform a curative limited resection of a focus without the risk of long-term diabetes. The exact preoperative planning by ¹⁸F-DOPA-PET/CT computer tomography allows laparoscopic operation in selected cases with the focus in the tail and limits necessity to open the pancreatic duct in cases with focus in the head. Patients with persistent CHI should be managed within a strong network of diagnostic, treatment, and research institutions.

Copyright © 2008 S. Karger AG, Basel

Introduction

Congenital hyperinsulinism (CHI, MIM 256450) is the most common cause of severe hypoglycemia in the neonatal and infancy period [1–5]. In the majority of persistent cases, mutations can be found in genes involved in β -cell regulation. Different types of CHI, which are indistinguishable by clinical symptoms, have been described by means of pancreatic venous sampling, histopathology and molecular genetics [6–9].

In recent years, considerable progress has been made in the morphological differentiation of CHI leading to different therapeutic approaches thereby avoiding unnecessary pancreatectomy in many cases. Preoperative analysis should both distinguish focal and diffuse type and localize the focal lesion within the pancreas as precisely as possible to guide limited pancreatic resection [10, 11]. In the present review we focus on the development of imaging techniques enabling exact preoperative judgment. Medline was searched using the MESH terms ‘congenital hyperinsulinism’ and ‘positron emission tomography’ to identify articles on these subjects. References from articles found in the original search were also used.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2008 S. Karger AG, Basel
0301–0163/08/0702–0065\$24.50/0

Accessible online at:
www.karger.com/hre

Dr. Klaus Mohnike
Otto-von-Guericke University Magdeburg
Leipziger Strasse 44, DE-39120 Magdeburg (Germany)
Tel. +49 391 67 24031, Fax +49 391 67 290038
E-Mail susann-empting@med.ovgu.de

Classification

Insulin secretion is controlled by a cascade of glucose enzymes in the β cells of the pancreatic islets. Neonatal-onset CHI is most often due to a defect in the potassium-sensitive ATP (K-ATP) channels of the β cell [12, 13]. The K-ATP channel is composed of a regulatory subunit, SUR1 (sulfonylurea receptor 1, encoded by ABCC8 – ATP-binding cassette, subfamily C, member 8) and the pore-forming channel unit Kir6.2 (inwardly rectifying potassium channel 6.2, encoded by KCNJ11 – potassium inwardly-rectifying channel, subfamily J, member 11). An increase in the cytoplasmatic ATP/ADP ratio leads to the closure of the channel, inhibiting potassium efflux from the cell. The resulting plasma membrane depolarization triggers calcium influx through voltage-gated calcium channels, finally leading to regulated insulin secretion. Mutations leading to a higher probability of the open condition of SUR have been detected in patients with neonatal diabetes, whereas the contrary is true in CHI [12, 14]. On the basis of histopathological image, a focal form has been described which is caused by a germline mutation of the paternal ABCC8/KCNJ11 allele and a somatic deletion of the maternal allele resulting in a hyperplastic adenomatous lesion containing functionally dysregulated β cells [9]. Histological differentiation between focal, diffuse and a third atypical type of CHI uses criteria of Rahier et al. [15, 16].

Diagnostic Algorithm

CHI is suspected if: (1) persistent or recurrent hypoglycemia (<2.5 – 3 mmol/l) is accompanied with detectable plasma insulin levels (>1 mU/l) together with inappropriately low plasma levels of ketone bodies, free fatty acid and branched chain amino acids; (2) high rates of intravenous glucose infusion (>10 mg/kg/min) are necessary to maintain blood glucose above 3 mmol/l, and (3) injection of 0.5 mg glucagon leads to an increase of 2–3 mmol/l glucose. Differential diagnosis includes known defects in insulin secretion. A cascade of enzymes in the β cells of the pancreatic islets plays a role in insulin secretion. Age at manifestation and diazoxide responsiveness have to be considered. In neonates the K-ATP channelopathies are more frequent and molecular genetic analysis for ABCC8 and KCNJ11 genes is helpful. Beyond the neonatal period, other defects in control of insulin secretion (summarized as metabolopathies) are more frequent. Glycemic response to 10–15 mg diazoxide/kg body weight

Fig. 1. ^{18}F -DOPA-PET/CT of a pancreatic focus in the head near venous confluents (red).

is usually the case in rare syndromes and metabolopathies [6].

For all persistent CHI, localization diagnosis by fluorine-18 L-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F -DOPA-PET) or integrated ^{18}F -DOPA-PET computer tomography (^{18}F -DOPA-PET/CT) is indicated in order to distinguish focal from diffuse forms (fig. 1). ^{18}F -DOPA-PET allows identification of a focal adenomatosis. With the new integrated ^{18}F -DOPA-PET/CT, a further step in localization for accurate preoperative planning is introduced (fig. 2).

Differential Therapy

The long-term outcome of infants with CHI is dependent on an effective prevention of hypoglycemic episodes to avert the high risk of permanent brain damage [8, 17–23]. Oral feeding is often difficult or even impossible in these children [24–26]. Immediate treatment modalities for CHI include high glucose infusion rates, continuous gastrostomy feeds and use of medications [25, 27–34]. Because of the difficulty to ensure normoglycemia by the conservative treatment modalities, the standard treatment for patients with early-onset CHI has in many centers been near-total (95%) pancreatectomy [4, 18, 35, 36]. However, it has now become apparent that 30–60% of neonatal-onset CHI is caused by the focal form of the disease [8, 9, 37, 38]. In most cases, only a tiny pancreatic

Table 1. ^{18}F -DOPA-PET or ^{18}F -DOPA-PET/CT diagnosis histological findings

Patients		Histological finding						comment	ref.
all	with histology	focal	ectopic	focal-atypical	insulinoma	diffuse	diffuse-atypical		
24	24	11		1		12		PET	61
50	50	18/24				24/24	2	PET	11
10	10	2			7			PET	64
1	1		1					PET	40
1	1		1					PET	39
49	24	14		1		7	2	PET	63
14	9	5				4		PET	60
1	1	1		0				PET-CT	65
10	10	9		1				PET-CT	10
83	24	18		1		4	1	PET-CT	Own data

lobulus of <1 cm is affected. Such a focus has been found in any part of the pancreas or sometimes even ectopically in the intestinal wall [10, 39, 40]. In these patients, limited pancreatic surgery can lead to complete cure. This emphasizes the need for exact preoperative diagnosis and localization of the focus in order to target the surgical approach.

Pancreatic Imaging

The pancreatic focus is rarely detectable by conventional MRI, CT or ultrasound. In view of the mostly normal macroscopic anatomy of the affected area, special techniques for the detection of the small pancreatic focus had to be based on the disturbed function of β cells [15, 41]. The basic principle is the uncontrolled insulin secretion in the affected area which leads to suppression of regulated insulin secretion by unaltered β cells. In the past, insulin gradients had been determined by pancreatic venous catheterization, which is an invasive and technically demanding procedure [36, 42, 43]. Other localization methods used in adults with insulinoma, e.g. pancreatic arterial calcium stimulation and the acute insulin response to intravenous glucose, calcium or tolbutamide, were only of limited value [44–46]. Alternatively, laparoscopy combined with multiple pancreatic biopsies has been proposed [35, 47].

In 2003, Otonkoski et al. [48] reported on PET using fluorine-18 labeled L-dihydroxyphenylalanine (^{18}F -DOPA) to accurately differentiate between focal and dif-

fuse type CHI. ^{18}F -DOPA-PET has been successfully used before to detect primary and metastatic pancreatic neuroectodermal tumors (NETs) [49, 50]. By replacing an ecological harmful radiosynthetic procedure, ^{18}F -DOPA has now been synthesized by an improved modification resulting in tracer yield with high specific activity [51].

Biochemical Background for Pancreatic Imaging

The neuroendocrine cells within the gastroenteropancreatic tract are accumulated and decarboxylate 5-hydroxytryptamine and L-3,4-dihydroxyphenylalanine (L-DOPA). In addition, an increased activity of L-DOPA decarboxylase was found to be a hallmark of NETs [52]. Likewise, pancreatic islets have been shown to take up L-DOPA and convert it into dopamine by the aromatic amino acid decarboxylase [53]. The physiological relevance of this metabolism is underscored by the finding that dopamine receptors are expressed in pancreatic β cells [54]. It should be mentioned that in Parkinson's disease, ^{18}F -DOPA-PET has been proven as a standardized technique to determine directly on the dopaminergic neurons the efficacy of drugs on disease activity [55].

De Lonlay et al. [56] compared the immunohistochemistry for DOPA decarboxylase, proinsulin and insulin in unaffected and hyperfunctional β -islets. The uptake of the positron emitting tracer ^{18}F -DOPA-PET was increased in β cells with a high rate of insulin synthesis and secretion compared to unaffected areas. So far,

Fig. 2. SUV 2.6 and 5.7 at ROI (see text for details).

L-DOPA can be regarded as a marker of aromatic amino acid decarboxylase activity.

Somatostatin receptor scintigraphy (SRS) with labeled somatostatin receptor analogs is the standard method for the detection and staging of NET. Comparative studies on imaging in PET showed superiority of DOPA-PET compared to SRS, at least for detection of lesions in the pancreatic tissue [57, 58]. In the study of Becherer et al. [57] in pancreatic tumours ^{18}F -DOPA-PET had a sensitivity of 92.3% and a specificity of 100%. In a prospective single-center study, ^{18}F -DOPA-PET with carbidopa pretreatment was superior to combined SRS and CT in imaging of carcinoid tumors and specifically in pancreas PET showed a better sensitivity than SRS and CT both in body region-based and lesion-based analysis [58].

Correlation of Histology and ^{18}F -DOPA-PET

The detection limit of PET imaging using [^{18}F]-fluorodeoxyglucose is equivalent to 10^5 – 10^6 cells (provided minimal tracer uptake of 50 Bq/cm³) and a diameter of approximately 1 mm [59]. Likewise, the smallest focal lesion detected on ^{18}F -DOPA-PET in Turku PET Centre measured 4×5 mm [60].

A sensitivity of 94% and a specificity of 100% have been reported when comparing PET and histology according to an international questionnaire and data published from the USA [61, 62]. However, surgery has not and will not be performed in all cases investigated by ^{18}F -DOPA-PET. Therefore, if PET shows a diffuse pattern, focal forms could go undiagnosed if they are medically controlled and not operated. In a controlled study,

Hardy et al. [11] reported that focal or diffuse type was correctly diagnosed by ^{18}F -DOPA-PET in 44 of 50 patients (88%). Six focal lesions were not detected on PET scan but found on initial biopsies. In fact, localization of the small affected pancreatic tissue has still been difficult leading to repeated laparoscopies in a few patients [10, 39, 40, 63]. Furthermore, a third rare atypical type has been defined histologically [9]. Atypical histology has been found in cases diagnosed before by ^{18}F -DOPA-PET as diffuse or focal form [63]. Lastly, drug interference with ^{18}F -DOPA metabolism has to be taken into account. It has been observed in single cases that somatostatin and diazoxide may not interfere with the ^{18}F -DOPA-PET. In contrast, glucagon has been known to interfere with β -cell activity and therefore it is recommended to stop this therapy 2 days before ^{18}F -DOPA-PET [63].

Imaging of the Pancreatic Focus

PET data are obtained in the axial axis and reconstructed in the coronal and sagittal axis. One has to distinguish the pancreatic focus from the surrounding organs in the upper abdomen (gallbladder, biliary duct, duodenum and kidneys). Different approaches had been used to identify the focus within the pancreas. This can be done by visually correlating PET findings to anatomical structures on corresponding axial MRI slices [60].

To further characterize the visual finding of the focus, the standard uptake value (SUV) at the region of interest (ROI) in PET images may be calculated [66]. Although general use of SUV needs validation in a large patient population, our initial experience suggests that this semi-quantitative index of ^{18}F -DOPA-PET metabolism is helpful and may increase confidence of visual interpretation. The ratio of SUV from focus versus mean of pancreas [ROI focal]/[ROI mean of other pancreas tissue] of >1.5 was predictive in most cases of focal disease in two analyses performed in different institutions (Turku and Berlin). However, excellent diagnostic accuracy has been reported even without the use of SUV calculations [11].

^{18}F -DOPA-PET allows differential diagnosis of focal and diffuse type CHI. However, the anatomical information provided by PET is limited compared to CT or MRI. Therefore, if the focal lesion is localized in the pancreatic head, extensive intraoperative search for the focus often requires substantial resection and dissection of the pancreatic duct. In these cases the remaining pancreas has to be drained by a Roux-en-Y reconstruction to preserve the pancreatic tail [41].

Fig. 3. Diagnosis and treatment CHI (see text for details).

The new integrated PET/CT method enables both exact anatomical and functional description of the pancreatic focus (fig. 1) [10]. Integrated PET/CT imaging may enable preservation of the pancreatic focus, due to exact anatomical and functional description of the pancreatic focus. The upper and middle abdomen is examined in the axial section in slices of 1 mm. The images are reconstructed in the coronal and sagittal plane to obtain a three-dimensional impression. The splenic artery, portal vein, superior mesenteric and inferior mesenteric artery as well as the duodenum are visualized by CT scan (fig. 1) [10]. In selected cases, particularly when the focus is in the tail, the exact preoperative planning by ^{18}F -DOPA-PET/CT allows laparoscopic resection (fig. 3).

Conclusions

^{18}F -DOPA-PET is an accurate and non-invasive technique to differentiate focal and diffuse type CHI. The high sensitivity of this method allows the surgeon to perform a curative limited resection of the focus without the long-term risk of diabetes. The use of integrated ^{18}F -DOPA-PET/CT allows laparoscopic operation in selected cases and limits the necessity to open the pancreatic duct in cases with the focus in the pancreatic head. ^{18}F -DOPA-PET or integrated ^{18}F -DOPA-PET/CT should be performed in all CHI patients requiring pancreatic surgery. These patients should be managed within a multidisciplinary network of diagnostic and therapeutic expertise [6–8, 21, 36, 41, 62].

References

- Hussain K: Congenital hyperinsulinism. *Semin Fetal Neonatal Med* 2005;10:369–376.
- De Lonlay P, Giurgea I, Touati G, Saudubray JM: Neonatal hypoglycaemia: aetiologies. *Semin Neonatol* 2004;9:49–58.
- Dekelbab BH, Sperling MA: Hyperinsulinemic hypoglycemia of infancy: the challenge continues. *Diabetes Metab Res Rev* 2004;20:189–195.
- Jack MM, Greer RM, Thomsett MJ, Walker RM, Bell JR, Choong C, Cowley DM, Herington AC, Cotterill AM: The outcome in Australian children with hyperinsulinism of infancy: early extensive surgery in severe cases lowers risk of diabetes. *Clin Endocrinol (Oxf)* 2003;58:355–364.
- Glaser B, Landau H, Permutt MA: Neonatal hyperinsulinism. *Trends Endocrinol Metab* 1999;10:55–61.
- Hussain K: Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. *Horm Res* 2008;69:2–13.
- Palladino AA, Bennett MJ, Stanley CA: Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. *Clin Chem* 2008;54:256–263.
- De Leon DD, Stanley CA: Mechanisms of disease: advances in diagnosis and treatment of hyperinsulinism in neonates. *Nat Clin Pract Endocrinol Metab* 2007;3:57–68.
- De Lonlay P, Simon A, Galmiche-Rolland L, Giurgea I, Verkarre V, Aigrain Y, Santiago-Ribeiro MJ, Polak M, Robert JJ, Bellanne-Chantelot C, Brunelle F, Nihoul-Fekete C, Jaubert F: Neonatal hyperinsulinism: clinicopathologic correlation. *Hum Pathol* 2007;38:387–399.
- Barthlen W, Blankenstein O, Mau H, Koch M, Hohne C, Mohnike W, Eberhard T, Fuechtner F, Lorenz-Depiereux B, Mohnike K: Evaluation of ^{18}F -DOPA PET-CT for surgery in focal congenital hyperinsulinism. *J Clin Endocrinol Metab* 2008;93:869–875.
- Hardy OT, Hernandez-Pampaloni M, Saffer JR, Scheuermann JS, Ernst LM, Freifelder R, Zhuang H, MacMullen C, Becker S, Adzick NS, Divgi C, Alavi A, Stanley CA: Accuracy of ^{18}F -fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism. *J Clin Endocrinol Metab* 2007;92:4706–4711.
- Ashcroft FM: The Walter B. Cannon Physiology in Perspective Lecture, 2007. ATP-sensitive K^+ channels and disease: from molecule to malady. *Am J Physiol* 2007;293:E880–E889.
- Hussain K: Insights in congenital hyperinsulinism. *Endocr Dev* 2007;11:106–121.
- Lin YW, Bushman JD, Yan FF, Haidar S, MacMullen C, Ganguly A, Stanley CA, Shyng SL: Destabilization of ATP-sensitive potassium channel activity by novel KCNJ11 mutations identified in congenital hyperinsulinism. *J Biol Chem* 2008;283:9146–9156.
- Rahier J, Guiot Y, Sempoux C: Persistent hyperinsulinaemic hypoglycaemia of infancy: a heterogeneous syndrome unrelated to nesidioblastosis. *Arch Dis Child Fetal Neonatal Ed* 2000;82:F108–F112.
- Sempoux C, Guiot Y, Jaubert F, Rahier J: Focal and diffuse forms of congenital hyperinsulinism: the keys for differential diagnosis. *Endocr Pathol* 2004;15:241–246.
- Al Nassar S, Sakati N, Al Ashwal A, Bin-Abbas B: Persistent hyperinsulinaemic hypoglycaemia of infancy in 43 children: long-term clinical and surgical follow-up. *Asian J Surg* 2006;29:207–211.
- Cherian MP, Abduljabbar MA: Persistent hyperinsulinemic hypoglycemia of infancy: long-term outcome following 95% pancreatectomy. *J Pediatr Endocrinol Metab* 2005;18:1441–1448.
- De Lonlay P, Fournet JC, Touati G, Groos MS, Martin D, Sevin C, Delagne V, Mayaud C, Chigot V, Sempoux C, Brusset MC, Laborde K, Bellanne-Chantelot C, Vassault A, Rahier J, Junien C, Brunelle F, Nihoul-Fekete C, Saudubray JM, Robert JJ: Heterogeneity of persistent hyperinsulinaemic hypoglycaemia. A series of 175 cases. *Eur J Pediatr* 2002;161:37–48.
- Filan PM, Inder TE, Cameron FJ, Kean MJ, Hunt RW: Neonatal hypoglycemia and occipital cerebral injury. *J Pediatr* 2006;148:552–555.
- Mazor-Aronovitch K, Gillis D, Lobel D, Hirsch HJ, Pinhas-Hamiel O, Modan-Moses D, Glaser B, Landau H: Long-term neurodevelopmental outcome in conservatively treated congenital hyperinsulinism. *Eur J Endocrinol* 2007;157:491–497.
- Meissner T, Wendel U, Burgard P, Schaeztle S, Mayatepek E: Long-term follow-up of 114 patients with congenital hyperinsulinism. *Eur J Endocrinol* 2003;149:43–51.
- Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA: Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. *J Pediatr Nurs* 2005;20:109–118.
- Bougneres PF, Landier F, Garnier P, Job JC, Chaussain JL: Treatment of insulin excess by continuous subcutaneous infusion of somatostatin and glucagon in an infant. *J Pediatr* 1985;106:792–794.

- 25 Glaser B, Hirsch HJ, Landau H: Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J Pediatr* 1993;123:644–650.
- 26 Lindley K, Knafelz D, St Louis D, Dunne M, Aynsley-Green A, Milla PJ: Surface electro-gastrographic evidence of foregut dysmotility in persistent hyperinsulinaemic hypoglycaemia of infancy (abstract). *J Physiol* 1997; 499:108.
- 27 Touati G, Poggi-Travert F, Ogier DB, Rahier J, Brunelle F, Nihoul-Fekete C, Czernichow P, Saudubray JM: Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. *Eur J Pediatr* 1998; 157:628–633.
- 28 Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA: Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993;123:637–643.
- 29 Plecko B, Stoeckler-Ipsiroglu S, Schober E, Harrer G, Mlynarik V, Gruber S, Moser E, Moeslinger D, Silgoner H, Ipsiroglu O: Oral β -hydroxybutyrate supplementation in two patients with hyperinsulinemic hypoglycemia: monitoring of β -hydroxybutyrate levels in blood and cerebrospinal fluid, and in the brain by in vivo magnetic resonance spectroscopy. *Pediatr Res* 2002;52:301–306.
- 30 Muller D, Zimmering M, Roehr CC: Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia? *Arch Dis Child* 2004;89:83–85.
- 31 Katz LE, Ferry RJ Jr, Stanley CA, Collett-Solberg PF, Baker L, Cohen P: Suppression of insulin oversecretion by subcutaneous recombinant human insulin-like growth factor I in children with congenital hyperinsulinism due to defective β -cell sulfonylurea receptor. *J Clin Endocrinol Metab* 1999;84: 3117–3124.
- 32 Hussain K, Aynsley-Green A, Stanley CA: Medications used in the treatment of hypoglycemia due to congenital hyperinsulinism of infancy. *Pediatr Endocrinol Rev* 2004; 2(suppl 1):163–167.
- 33 Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fekete C, Lonlay-Debeney P, Brunelle F, Otonkoski T, Thornton P, Lindley KJ: Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000;82:F98–F107.
- 34 Mohnike K, Blankenstein O, Pflutzner A, Poetsch S, Schober E, Steiner S, Hardy OT, Grimberg A, van Waarde WM: Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. *Horm Res* 2008 (accepted).
- 35 Suchi M, Thornton PS, Adzick NS, MacMullen C, Ganguly A, Stanley CA, Ruchelli ED: Congenital hyperinsulinism: intraoperative biopsy interpretation can direct the extent of pancreatectomy. *Am J Surg Pathol* 2004;28: 1326–1335.
- 36 Lovvorn HN III, Nance ML, Ferry RJ Jr, Stolte L, Baker L, O'Neill JA Jr, Schnaufer L, Stanley CA, Adzick NS: Congenital hyperinsulinism and the surgeon: lessons learned over 35 years. *J Pediatr Surg* 1999;34:786–792.
- 37 Sperling MA: PET scanning for infants with HHI: a small step for affected infants, a giant leap for the field. *J Pediatr* 2007;150:122–124.
- 38 Giurgea I, Sempoux C, Bellanne-Chantelot C, Ribeiro M, Hubert L, Boddaert N, Saudubray JM, Robert JJ, Brunelle F, Rahier J, Jaubert F, Nihoul-Fekete C, de Lonlay P: The Knudson's two-hit model and timing of somatic mutation may account for the phenotypic diversity of focal congenital hyperinsulinism. *J Clin Endocrinol Metab* 2006;91: 4118–4123.
- 39 Hussain K, Seppanen M, Nanto-Salonen K, Adzick NS, Stanley CA, Thornton P, Minn H: The diagnosis of ectopic focal hyperinsulinism of infancy with [^{18}F]-DOPA positron emission tomography. *J Clin Endocrinol Metab* 2006;91:2839–2842.
- 40 Peranteau WH, Bathaui SM, Pawel B, Hardy O, Alavi A, Stanley CA, Adzick NS: 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.
- 41 Fekete CN, de Lonlay P, Jaubert F, Rahier J, Brunelle F, Saudubray JM: The surgical management of congenital hyperinsulinemic hypoglycemia in infancy. *J Pediatr Surg* 2004; 39:267–269.
- 42 Brunelle F, Negre V, Barth MO, Fekete CN, Czernichow P, Saudubray JM, Kuntz F, Tach T, L'Allemand D: Pancreatic venous samplings in infants and children with primary hyperinsulinism. *Pediatr Radiol* 1989;19: 100–103.
- 43 Dubois J, Brunelle F, Touati G, Sebag G, Nuttin C, Thach T, Nikoul-Fekete C, Rahier J, Saudubray JM: Hyperinsulinism in children: diagnostic value of pancreatic venous sampling correlated with clinical, pathological and surgical outcome in 25 cases. *Pediatr Radiol* 1995;25:512–516.
- 44 Chigot V, de Lonlay P, Nassogne MC, Laborde K, Delagne V, Fournet JC, Nihoul-Fekete C, Saudubray JM, Brunelle F: Pancreatic arterial calcium stimulation in the diagnosis and localisation of persistent hyperinsulinemic hypoglycaemia of infancy. *Pediatr Radiol* 2001;31:650–655.
- 45 Giurgea I, Laborde K, Touati G, Bellanne-Chantelot C, Nassogne MC, Sempoux C, Jaubert F, Khoa N, Chigot V, Rahier J, Brunelle F, Nihoul-Fekete C, Dunne MJ, Stanley C, Saudubray JM, Robert JJ, de Lonlay P: Acute insulin responses to calcium and tolbutamide do not differentiate focal from diffuse congenital hyperinsulinism. *J Clin Endocrinol Metab* 2004;89:925–929.
- 46 Stanley CA, Thornton PS, Ganguly A, MacMullen C, Underwood P, Bhatia P, Steinkrauss L, Wanner L, Kaye R, Ruchelli E, Suchi M, Adzick NS: 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.
- 47 Adzick NS, Thornton PS, Stanley CA, Kaye RD, Ruchelli E: A multidisciplinary approach to the focal form of congenital hyperinsulinism leads to successful treatment by partial pancreatectomy. *J Pediatr Surg* 2004; 39:270–275.
- 48 Otonkoski T, Veijola R, Huopio H, Nanto-Salonen K, Tapanainen P, De Lonlay J, Fekete C, Brunelle F, Minn H, Nuutila P: Diagnosis of focal persistent hyperinsulinism of infancy with ^{18}F -fluoro-L-L-DOPA PET. *Horm Res* 2003;60(suppl 2):2.
- 49 Ahlstrom H, Eriksson B, Bergstrom M, Bjurling P, Langstrom B, Oberg K: Pancreatic neuroendocrine tumors: diagnosis with PET. *Radiology* 1995;195:333–337.
- 50 Hoegerle S, Schneider B, Kraft A, Moser E, Nitzsche EU: Imaging of a metastatic gastrointestinal carcinoid by ^{18}F -DOPA positron emission tomography. *Nuklearmedizin* 1999;38:127–130.
- 51 Fuchtnr F, Zessin J, Mading P, Wust F: Aspects of 6- ^{18}F -fluoro-L-DOPA preparation. Deuteriochloroform as a substitute solvent for Freon 11. *Nuklearmedizin* 2008;47:62–64.
- 52 Gazdar AF, Helman LJ, Israel MA, Russell EK, Linnoila RI, Mulshine JL, Schuller HM, Park JG: Expression of neuroendocrine cell markers L-DOPA decarboxylase, chromogranin A, and dense core granules in human tumors of endocrine and nonendocrine origin. *Cancer Res* 1988;48:4078–4082.
- 53 Lindstrom P: Aromatic L-amino-acid decarboxylase activity in mouse pancreatic islets. *Biochim Biophys Acta* 1986;884:276–281.
- 54 Rubi B, Ljubicic S, Pournourmohammadi S, Carobbio S, Armanet M, Bartley C, Maechler P: Dopamine D_2 -like receptors are expressed in pancreatic β cells and mediate inhibition of insulin secretion. *J Biol Chem* 2005;280: 36824–36832.
- 55 Whone AL, Bailey DL, Remy P, Pavese N, Brooks DJ: A technique for standardized central analysis of 6- ^{18}F -fluoro-L-DOPA PET data from a multicenter study. *J Nucl Med* 2004;45:1135–1145.
- 56 De Lonlay P, Simon-Carre A, Ribeiro MJ, Boddaert N, Giurgea I, Laborde K, Bellanne-Chantelot C, Verkarre V, Polak M, Rahier J, Syrota A, Seidenwurm D, Nihoul-Fekete C, Robert JJ, Brunelle F, Jaubert F: Congenital hyperinsulinism: pancreatic [^{18}F]-fluoro-L-dihydroxyphenylalanine (DOPA) positron emission tomography and immunohistochemistry study of DOPA decarboxylase and insulin secretion. *J Clin Endocrinol Metab* 2006;91:933–940.

- 57 Becherer A, Szabo M, Karanikas G, Wunderbaldinger P, Angelberger P, Raderer M, Kurtaran A, Dudczak R, Kletter K: Imaging of advanced neuroendocrine tumors with ^{18}F -FDOPA PET. *J Nucl Med* 2004;45:1161–1167.
- 58 Koopmans KP, de Vries EG, Kema IP, Elsinga PH, Neels OC, Sluiter WJ, van der Horst-Schrivers AN, Jager PL: Staging of carcinoid tumours with ^{18}F -DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol* 2006;7:728–734.
- 59 Fischer BM, Olsen MW, Ley CD, Klausen TL, Mortensen J, Hojgaard L, Kristjansen PE: How few cancer cells can be detected by positron emission tomography? A frequent question addressed by an in vitro study. *Eur J Nucl Med Mol Imaging* 2006;33:697–702.
- 60 Otonkoski T, Nanto-Salonen K, Seppanen M, Veijola R, Huopio H, Hussain K, Tapanainen P, Eskola O, Parkkola R, Ekstrom K, Guiot Y, Rahier J, Laakso M, Rintala R, Nuutila P, Minn H: Noninvasive diagnosis of focal hyperinsulinism of infancy with ^{18}F -DOPA positron emission tomography. *Diabetes* 2006;55:13–18.
- 61 Hardy OT, Hernandez-Pampaloni M, Saffer JR, Suchi M, Ruchelli E, Zhuang H, Ganguly A, Freifelder R, Adzick NS, Alavi A, Stanley CA: Diagnosis and localization of focal congenital hyperinsulinism by ^{18}F -fluorodopa PET scan. *J Pediatr* 2007;150:140–145.
- 62 Mohnike K, Blankenstein O, Christesen HT, De Lonlay J, Hussain K, Koopmans KP, Minn H, Mohnike W, Mutair A, Otonkoski T, Rahier J, Ribeiro M, Schoenle E, Fekete CN: Proposal for a standardized protocol for ^{18}F -DOPA-PET (PET/CT) in congenital hyperinsulinism. *Horm Res* 2006;66:40–42.
- 63 Ribeiro MJ, Boddaert N, Bellanne-Chantelot C, Bourgeois S, Valayannopoulos V, Delzescaux T, Jaubert F, Nihoul-Fekete C, Brunelle F, de Lonlay P: The added value of ^{18}F fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy: a retrospective study involving 49 children. *Eur J Nucl Med Mol Imaging* 2007;34:2120–2128.
- 64 Kauhanen S, Seppanen M, Minn H, Gullichsen R, Salonen A, Alanen K, Parkkola R, Solin O, Bergman J, Sane T, Salmi J, Valimaki M, Nuutila P: Fluorine-18-L-dihydroxyphenylalanine positron emission tomography as a tool to localize an insulinoma or β -cell hyperplasia in adult patients. *J Clin Endocrinol Metab* 2007;92:1237–1244.
- 65 Kapoor RR, Gilbert C, Mohnike K, Blankenstein O, Fuechtner F, Hussain K: Congenital hyperinsulinism: ^{18}F DOPA PET/CT scan of a focal lesion in the head of the pancreas. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F166.
- 66 Minn H, Leskinen-Kallio S, Lindholm P, Bergman J, Ruotsalainen U, Teras M, Haaparanta M: ^{18}F fluorodeoxyglucose uptake in tumors: kinetic versus steady-state methods with reference to plasma insulin. *J Comput Assist Tomogr* 1993;17:115–123.