Mini Review

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

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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.
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 germ-line 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 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 (18F-DOPA-PET) or integrated 18F-DOPA-PET computer tomography (18F-DOPA-PET/CT) is indicated in order to distinguish focal from diffuse forms (fig. 1). 18F-DOPA-PET allows identification of a focal adenomatosis. With the new integrated 18F-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
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 (18F-DOPA) to accurately differentiate between focal and diffuse type CHI. 18F-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, 18F-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, 18F-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 18F-DOPA-PET was increased in β cells with a high rate of insulin synthesis and secretion compared to unaffected areas. So far,
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, 18F-DOPA-PET had a sensitivity of 92.3% and a specificity of 100%. In a prospective single-center study, 18F-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 18F-DOPA-PET**

The detection limit of PET imaging using [18F]-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 18F-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 been performed in all cases investigated by 18F-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 18F-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 18F-DOPA-PET as diffuse or focal form [63]. Lastly, drug interference with 18F-DOPA metabolism has to be taken into account. It has been observed in single cases that somatostatin and diazoxide may not interfere with the 18F-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 18F-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 18F-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].

18F-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. 2. SUV 2.6 and 5.7 at ROI (see text for details).](image-url)
Distinguish between focal or diffuse form

18F-DOPA-PET or 18F-DOPA-PET/CT

Focal

Conservative treatment (incl. octreotide, frequent meals, PEG)

If no euglycemia (6 h fasting)
alternatively subcutaneous glucagon or pancreatectomy (near-total or total)

Diffuse

Enucleation of focal lesion

Distinguish between focal or diffuse form

Treatment of CHI

Prevention of recurrent hypoglycemia
i.v. glucose infusion, glucagon [1–(3) mg/day]
Oral feedings
First choice of medical treatment
- Diazoxide (10–15 mg/kg/day)

If diazoxides unresponsive
Next steps
- Octreotide (10–50 μg/day)
- Nifedipine (0.5–2 mg/day)

Glycemic response to glucagon
(injection of 0.5 mg leads to an increase of 2–3 mmol/l glucose)

Diagnosis of CHI

- Persistent or recurrent hypoglycemia (<2.5–3 mmol/l)
- Detectable plasma insulin levels (>1 mU/l)
- Low plasma levels of ketone bodies, free fatty acid and branched chain amino acids
- High rates of intravenous glucose infusion (>10 mg/kg/min)

Follow-up
- Growth
- Neurological/psychomotoric development
- Development of diabetes mellitus

Prevention of recurrent hypoglycemia
Persistent or recurrent hypoglycemia (<2.5–3 mmol/l)
Detectable plasma insulin levels (>1 mU/l)
Low plasma levels of ketone bodies, free fatty acid and branched chain amino acids
High rates of intravenous glucose infusion (>10 mg/kg/min)

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].

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