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Original Article

PET/CT in congenital hyperinsulinism: transforming patient's lives by molecular hybrid imaging

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Abstract: Congenital hyperinsulinism (HI) is a life-threatening condition characterized by severe and recurrent episodes of hypoglycaemia due to defects in key genes involved in regulating insulin secretion. The delay in diagnosis and inappropriate management of HI lead to high risk of permanent hypoglycemic brain injury. The management of HI is challenging as each form of HI (focal, diffuse, and atypical) requires its own therapeutic strategy. In HI diagnostic work-up, integrated PET/CT scan is currently the first-line imaging technique allowing to differentiate between diffuse and focal form and, in the latter case, to localize the focus within the pancreas with high precision. Only in focal HI partial pancreatectomy is the treatment of choice and a curative surgical treatment means a real chance of transforming patient's lives and HI patient's future. The aim of this review is to discuss the role of PET/CT imaging in HI scenario, its technical advantages and limitations and how successful surgery is strongly dependent on accurate preoperative assessment (genetic analysis and PET/CT scan). A multidisciplinary approach in HI diagnosis and treatment inside a single team (involving different expertise) allows to manage children safely and properly, supporting their families in an organized care network.

Keywords: Congenital hyperinsulinism, PET/CT, molecular hybrid imaging, DOPA, pediatric

Introduction

Congenital hyperinsulinism (HI), although rare, has a high clinical relevance representing the most common cause of persistent and severe hypoglycemia in infants and children with a broad range of possible complications (including death) or an unpredictable spontaneous cure. The reported incidence in the United States is 1:25000-1:50000 live births [1], and 1:2500 in areas with high rates of consanguinity such as Saudi Arabia [2].

HI is due to a primary defect of the pancreatic β-cell characterized by an abnormal insulin-over secretion leading to hypoketotic hypoglycemia in early childhood [3]. Histologically there are two main types of HI, focal (in case of a limited lesion of β-cell hyperplasia within a restricted area of the pancreas) and diffuse (when all β-cell are involved throughout the pancreas). This scenario becomes more complex considering the atypical form (characterized by a more extensive segmental mosaic pattern based on a peculiar histopathological form with an unknown molecular basis) [4-6] as well as for ectopic [7] or multiple [8] focal lesions. HI is a real challenging disease with multifaceted aspects due to its heterogeneous nature from a histopathology, genetic and clinical perspective [9]. Differential diagnosis between focal and diffuse HI is a crucial step. Indeed, partial pancreatectomy is the elective procedure for focal HI allowing the complete recovery from hypoglycemia. Focal lesions are not usually detected by conventional imaging techniques, including

computed tomography or magnetic resonance imaging [10]. In the past, interventional radiologic procedures (e.g. pancreatic venous sampling, arterial calcium stimulation and hepatic venous sampling) have been used, however because of their invasiveness and high radiation exposure they were abandoned [3, 11]. The role of nuclear medicine and the gain of molecular hybrid imaging in this selected but clinically relevant field have been well demonstrated in several studies since 2003 [1, 12-15]. In nuclear medicine field, ^{18}fluorine-fluorodihydroxyphenylalanine (^{18}F-DOPA) PET/CT is currently the main nuclear medicine modality in differentiation focal from diffuse HI [1], representing a perfect example of clinical impact of molecular imaging. ^{18}F-DOPA PET imaging reflects the activity of neuroendocrine cells present in the pancreas based on their affinity for taking up amino acid precursors. ^{18}F-DOPA shares the same mechanism of uptake, conversion and storage of L-DOPA, allowing imaging of pancreatic β-cells. Focal lesion appears as a localized area of intense uptake, clearly detectable respect to the background lower-level activity in the surrounding normal pancreas. Otherwise, diffuse HI disease involves all pancreatic β-cells and ^{18}F-DOPA PET imaging shows a homogeneous ^{18}F-DOPA uptake throughout the pancreas [1]. A different type of HI means a different type of clinical approach since focal HI can be treat by surgery while medical therapy (mainly diazoxide, octreotide) is usually used for diffuse form (except for patients unresponding to medical therapy) [16]. Therefore, this method is very accurate in evaluation of eligible patients to surgery showing a real theranostic value.

Other tracers are under investigation to overcome ^{18}F-DOPA imaging limits mainly due to the radiotracer unavailability in some Countries as for the technical difficulties related to its synthesis [17, 18].

Considering the lifelong sequelae (brain damage with neurodisability and side effects due to chronic medical treatment) the most important endpoint for patients affected by HI is improving clinical outcome with an accurate differential diagnosis and a prompt adequate treatment [19].

The main goal of all medical team involved in HI care is to select patients with focal form. With this aim, the hybrid molecular imaging gives to the child a real chance of deep life change improving quality of life and clinical outcome by curative surgical treatment.

Clinical and genetic diagnosis of HI has a pivotal role in the management of these patients allowing an accurate selection of those who can benefit from ^{18}F-DOPA PET/CT imaging. Subsequently, hybrid imaging (providing molecular biological data integrated with anatomical information) drives clinical approach from diagnosis to surgical treatment in case of suspected focal HI.

Clinical management of patients affected by HI requires a high specific expertise and great efforts to reach an adequate glucose balance by medications, nutrition, and surgical treatment (when suitable). A multidisciplinary approach is the key strategy to go from diagnosis to treatment preventing the high risk of irreversible brain damage secondary to hypoglycemia [10, 20].

^{18}F-DOPA PET/CT imaging

Appropriate use criteria based on genetic screening

Current diagnostic algorithms in persistent HI are based on diagnostic tools including biochemical assays, genetic tests and ^{18}F-DOPA PET/CT imaging. Hypoglycemia is the main feature of HI, permanent both in the fasting and the post-prandial states, associated with the finding of unsuppressed insulin and/or with indirect signs of inappropriate insulin excess (such as suppressed circulating non-esterified fatty acids -NEFA, hypoketonemia, hyperglycemic response to glucagon and high glucose demand) [3, 16]. Genetic tests contribute in this scenario to ensure appropriate use criteria of ^{18}F-DOPA PET/CT imaging in HI [21, 22]. Knowledge of genetic features helps to select patients who can benefit from ^{18}F-DOPA PET/CT, representing a tailored approach of nuclear medicine imaging. Mutations in the genes encoding for the subunits of the K_{ATP} channel are associated with two histological aspects of the endocrine pancreas. A diffuse form extended to all pancreatic β-cells, inherited as either autosomal recessive or dominant trait, and a focal form, which results from the combination of a paternally inherited germinal mutation and a somatic loss of heterozygosity of the mater-

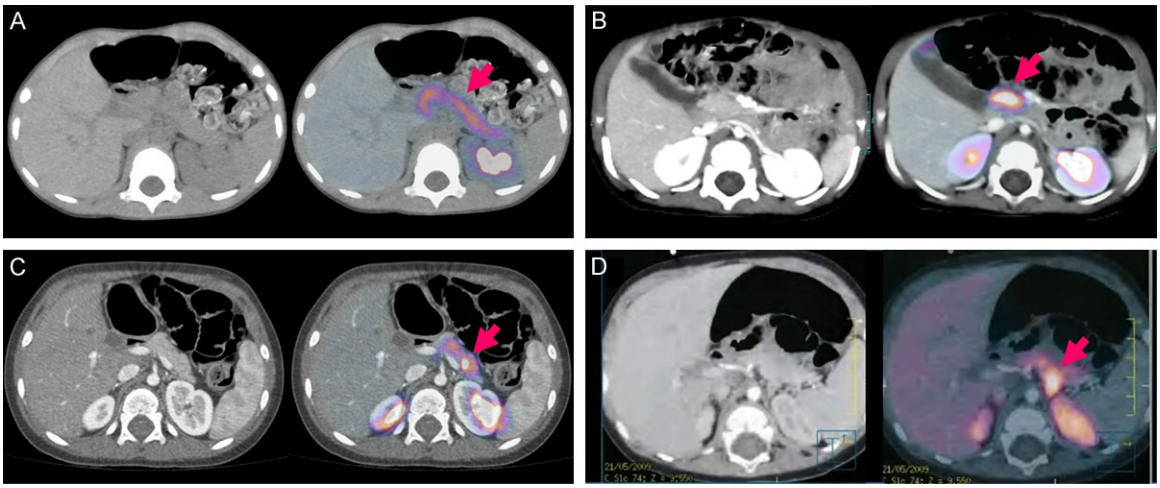

Figure 1. ^{18}F-DOPA PET/TC - diffuse (A) and focal (B-D) pattern. (A) Axial F-DOPA PET image shows a uniform ^{18}F-DOPA uptake throughout the pancreas. (B-D) PET/CT scan clearly show a focal ^{18}F-DOPA uptake in the pancreatic area (corresponding to head, body, and tail, respectively, as indicated by the red arrow). In all cases, after partial pancreatectomy, PET/CT findings were pathologically confirmed resulting in a complete remission of hypoglycemia. In (D), posterior exophytic lesion in pancreatic tail (localized near to left kidney) could represent a challenging position of focal lesion but hybrid imaging ruled out any interpretative doubts about a possible false positive result (as for urinary excretion pitfall). In all reported cases of focal HI, quantitative analysis confirmed visual interpretation (resulting in SUV ratio >1.2).

nal allele in a focused area of the pancreas [23]. Several other gene mutations are involved in the pathogenesis of HI, and give rise to diffuse forms [16]. Gene mutations associated to focal disease have a positive predicted value of 94% for focal HI and PET/CT scan is indicated to confirm the diagnosis localizing the focal lesion for preoperative planning [1]. When genetic analysis is consistent with diffuse disease, ^{18}F-DOPA PET/CT is not indicated avoiding a useless procedure, which requires a significant radiation exposure and anesthesia. Therefore, genetic and PET imaging diagnosis of focal HI allows a complete remission of disease by surgery, avoiding irreversible brain damage high risks, the chronic medical therapy discomfort (with relative side-effects) and the strict daily glucose level monitoring [16].

Molecular hybrid imaging

PET imaging is a valuable tool providing a clear picture of pancreatic β-cell metabolism due to the high specificity of ^{18}F-DOPA, an analogue of dopamine precursor labelled with a positron-emitting compound, useful for tracking tracer distribution within the pancreas or in abdominal ectopic site.

The principle of this imaging technique is related to the affinity of pancreatic β-cell, like other neuroendocrine cells, for taking up and concentrating DOPA tracer as dopamine. In diffuse HI, ^{18}F-DOPA uptake is uniform throughout the pancreas, whereas in focal HI the focal lesion can be identified by greater uptake than the surrounding normal pancreas [24] (**Figure 1A-D**). Focal and diffuse HI share the same clinical presentation and conventional noninvasive radiological imaging studies are usually not helpful in distinguishing between the two forms due to the lack of morphologic alterations in pancreatic structure [10].

As reported by several studies, ^{18}F-DOPA PET imaging allows differentiating between the diffuse and focal form and, in the latter case, to localize the focus within the pancreas with high precision [11, 23].

In the past, the distinction before surgery between the two major forms of HI was based on the use of invasive radiological techniques, able to obtain a map of glucose, insulin and C peptide concentrations within the whole pancreas by pancreatic venous catheterization (collecting venous blood samples with possible additional intravenous stimulation of insulin secretion by calcium and tolbutamide). These invasive methods require the maintenance of controlled hypoglycemia during the procedure, the suspension of medical therapy, and general

anesthesia. These considerable technical difficulties and the high risks associated with these methods have resulted in a limited diagnostic widespread in very few centres with the necessary acquired experience [25].

Therefore, the development of a less invasive examination such as ^{18}F-DOPA PET/CT imaging represents a major step forward in HI diagnostic-therapeutic decision-making process providing a bright light on HI disease.

A standardized acquisition protocol for ^{18}F-DOPA PET investigation was proposed by Mohnike et al. in 2006 [26]. For this examination, the patient needs to fast for 4 hours before test, stopping glucagon (for at least 48 hours) achieving a glycemic control by intravenous glucose infusion. ^{18}F-DOPA PET scan is generally performed under general anesthesia (except in older collaborating children) and the continuous assistance of pediatric metabolic physician. An activity of 4 MBq/kg of ^{18}F-DOPA is intravenously injected, and PET scanning of upper and middle abdomen should be performed before the appearance of biliary elimination artifacts (30-45 minutes from tracer injection even if there is no consensus concerning the optimal acquisition time). LIST-MODE data acquisition could be helpful using a "dynamic" PET imaging up to 15 minutes of registration. This modality can be used to select images before bile excretion or to reduce motion artefacts as well [27]. In the younger patients, the obtained images using a brain-dedicated field of view show a high resolution quality; this technical tip can optimize imaging performance in the small child abdomen, as well in the brain (unpublished data).

PET is firstly carried out with a low-dose CT scan and PET imaging is visually analyzed [28] Barthlen et al. [15] introduced a simultaneously recorded contrast-enhanced CT imaging to determine vascular landmarks before surgery for a more accurate localization of focal lesion. From the surgical point of view, the value of the functional imaging is closely related to the high technical difficulty of pancreatic surgery performed on extremely young patients - especially in case of focal lesion located in the pancreatic head or in the uncinate process. The anatomical and functional information provided by PET-CT imaging can guide to a non-destructive intervention preserving pancreatic-duodenal continuity or vice-versa to the duodenocephalopancreatectomy (one of the most complex and difficult abodominal operation to carry out in pediatric population). As reported by Von Rohden et al. [29], the intraoperative high-resolution sonography could also help the pediatric surgeon to visualize the focal lesion preoperatively localized by PET/CT during the surgical procedure. This useful intraoperative diagnostic tool could provide peculiar information detecting irregular shape of the focal area due to filiform processes into the surrounding pancreatic tissue.

New hybrid PET/CT systems allow great advances in optimizing pediatric radiation doses using "child-size CT protocol" [27].

Using histology as reference standard, ^{18}F-DOPA PET/CT imaging demonstrates high sensitivity (ranging from 75% to 100%) and specificity (ranging from 88% to 100%) in differentiating between focal and diffuse HI [1, 11]. In addition, the advanced integrated ^{18}F-DOPA PET/CT imaging allows an accurate preoperative planning describing the exact anatomical and functional picture of the pancreatic focus, with an accuracy of localization of the focal lesion greater than 90% [1]. Given the demonstrated high diagnostic performance, ^{18}F-DOPA PET/CT is considered the first-line imaging method in focal HI diagnosis and localization [11], replacing interventional radiology techniques used in the past (invasive, technically difficult with high radiation exposure and lower diagnostic accuracy) [30].

However, possible limitations of this functional imaging technique should be kept in mind considering that the focal lesion could be not clearly detectable due to its size, shape or location [1, 11, 31]. False negative results could be related to the focal lesion size, too small or too large. The smallest focal lesion detected by ^{18}F-DOPA PET measured 4 × 5 mm at histology [12] but when the small lesion uptake is like the rest of the gland, lesion to background activity ratio could be insufficient and PET scan could be interpreted as a diffuse pattern. Conversely, also a large focal lesion occupying 80-90% of the pancreas could be falsely suggestive of a diffuse form [31, 32]. Irregular shape of the focal lesion could make PET interpretation confounding as reported by Laje et al. [33] who described a not clearly identifiable flat leaflike

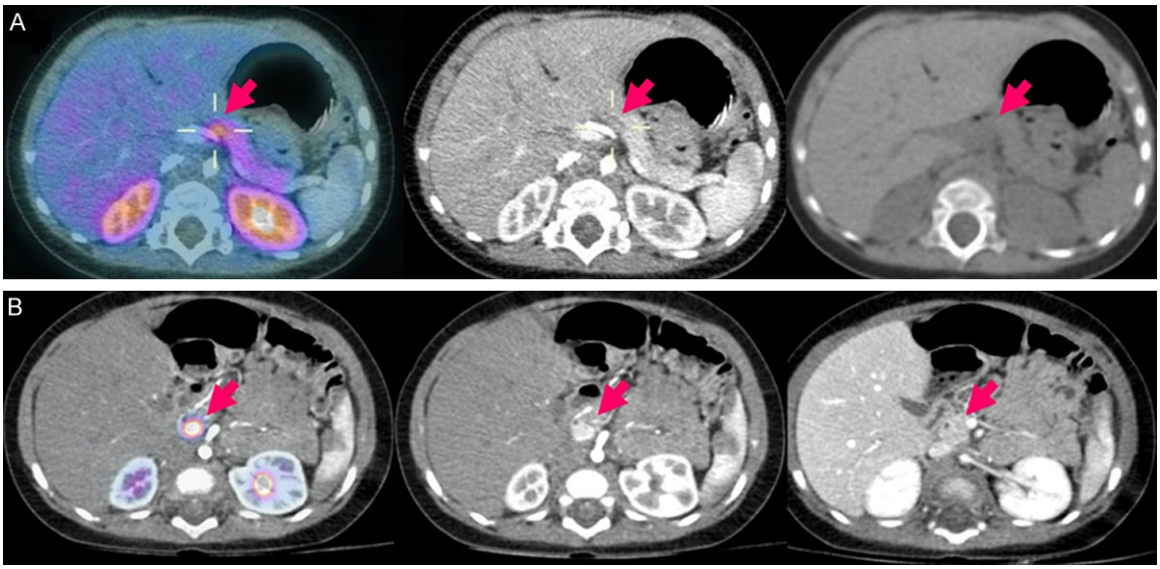

Figure 2. Contrast-enhanced CT imaging: unusual findings in focal HI pattern. Added value of abdominal contrast-enhanced CT scan in focal form of HI (confirmed by histology) detected by ^{18}F-DOPA PET. A. HYPO pattern: PET/CT imaging shows a focal area of increased dopaminergic activity corresponding to isthmus with respect to the rest of the pancreas (SUV ratio was slightly higher than 1.2). Contrast-enhanced CT imaging reveals a small area of reduced enhancement (maximum axial diameter of 9 mm) located laterally to the proximal tract of hepatic artery, corresponding to the focal lesion detected by ^{18}F-DOPA PET in the pancreatic isthmus. This finding isn't detectable assessing basal low-dose CT imaging. B. HYPER pattern: PET/CT images show a "bright" area of intense ^{18}F-DOPA uptake localized within the entire pancreatic head, with a SUV ratio indicative of focal lesion. Abdominal contrast-enhanced CT imaging shows an increased contrast enhancement in the head of pancreas considering arterial phase while this finding is not detectable in portal phase. Contrast-enhanced CT scan (as for other conventional radiological methods) is usually unable to identify the focal HI lesion due to the absence of structural alterations. An accurate analysis of hybrid imaging data helps to obtain a correct localization of focal lesion (detected by PET scan) guiding surgical resection. Looking further ahead, a careful assessment of all hybrid imaging data could lead to discover uncommon findings increasing diagnostic confidence (especially for small/large HI focal lesion) and improving the knowledge of a challenging disease with heterogeneous features.

focal lesion on the surface of the pancreas. Small focal lesions located in the pancreatic tail could be missed due to the masking effect of excreted tracer visualized in the adjacent upper pole of left kidney. Pancreatic head is another critical location in PET imaging assessing when heterogeneous tracer distribution is associated to a physiologic relative increased activity (due to the larger volume of pancreatic head respect to the rest of the pancreas) [11, 31]. The rarity of the disease and the complexity of the diagnostic-therapeutic decision-making process justify the concentration of patients in specialized centers with specific know-how and expertise.

Quantitative analysis using the DOPA uptake ratio (SUVr, SUV max of the lesion vs SUV max of the rest "normal" pancreas) could integrate visual PET imaging assessment leading to an increased diagnostic confidence, as reported by Otonkoski (SUVr >1.5) [12] and Ribeiro (SUVr >1.2) [24].

Furthermore, in hybrid imaging era, all available imaging data should be carefully assessed because, as reported by Hashimoto et al. [34], unexpected findings could be detected by contrast-enhanced computed tomography imaging in the site of the focal lesion visible at PET scan. In **Figure 2A** and **2B** we reported two further examples of unusual findings detected by contrast-enhanced CT imaging in focal HI PET pattern. These clinical cases, based on the personal experience of our HI team, confirm the possible added value of abdominal contrast-enhanced CT scan in focal forms detected by ^{18}F-DOPA PET.

Current integrated PET/CT imaging equipped with high resolution system allows a high image quality visualizing a detailed anatomy also in case of small anatomical structures in extremely young children. These advances in diagnostic imaging are very useful to avoid one of the pitfalls of interpretation due to focal uptake in the pancreatic head secondary to physiological bile

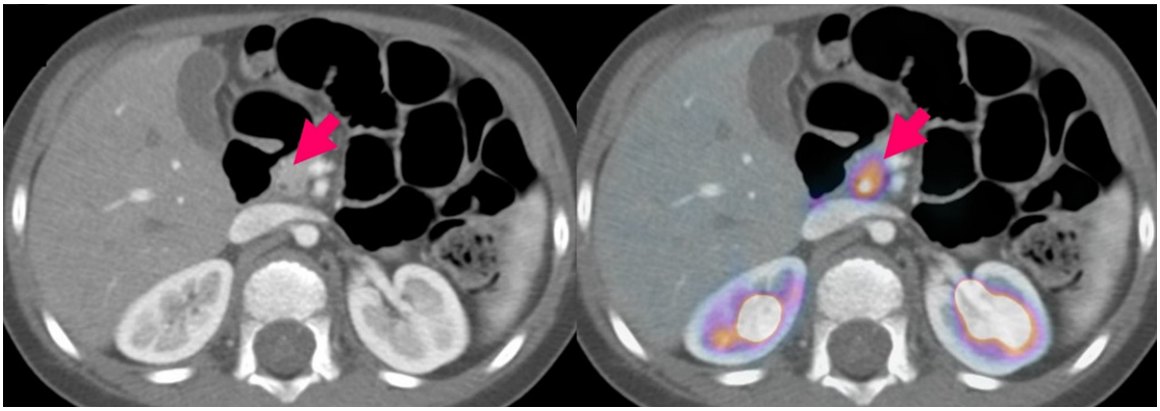

Figure 3. ^{18}F-DOPA PET/TC pitfall: tracer stasis in bile duct. One of the pitfalls of interpretation is due to physiological bile excretion of tracer with possible ^{18}F-DOPA stasis in common bile duct. PET scanning of abdomen before 45-60 minutes (from tracer injection) sometimes doesn't avoid this technical aspect resulting in an area of increased uptake in the head of pancreas. Integrated PET/CT images are helpful in the evaluation of this physiologic uptake pattern locating the hot spot in correspondence to common bile duct (as clearly detectable by current PET-CT imaging equipped with high resolution system).

excretion of tracer in common bile duct [31] (**Figure 3**).

Despite these technical advances, rarer forms of HI continue to be a diagnostic challenge in clinical practice. Atypical forms are generally described as non-focal and non-diffuse form. Based on a review of pathological reports, Capito et al. [35] have identified two varieties of atypical forms: extensive focal forms and segmental mosaic forms. In both cases ^{18}F-DOPA PET/CT presents diagnostic limitations (32, 36) showing us that we have much more to learn about this heterogeneous disease. Although rare, atypical forms of HI show a significant clinical impact representing up to 10% of all HI patients undergoing subtotal pancreatectomy for medically unresponsive HI [4]. Furthermore, bifocal forms in the same area may be missed on PET scan due to the PET spatial resolution converging in a unique hot spot [24]. Bifocal foci could have a significant clinical impact during surgical procedure leading to an increased risk of an uncomplete lesion removal.

Among the complex heterogeneity of focal HI, we have also to consider extremely rare clinical conditions, as ectopic or multiple ectopic focal lesions [7, 8].

In the HI management, factitious hyperinsulinism leading to pancreatectomy has been reported in severe forms of Munchausen Syndrome by Proxy [37]. As shown in **Figure 4A** and **4B**, PET/CT imaging can play a role ruling out the presence of hyperfunctioning pancreatic or ectopic focal lesions responsible for the hyperinsulinism (including focal HI or insulinoma).

Assessing the utility of hybrid imaging modalities in the clinical management of patients affected by HI, ^{18}F-DOPA PET/MRI could be a promising preoperative tool to detect and localize focal lesions in the pancreas (ClinicalTrials.gov Identifier: NCT05088798). PET/MRI has a significantly lower radiation burden compared to PET/CT, as MRI does not have any radiation exposure. The reduction of the radiation dose from PET/MRI is particularly beneficial to the pediatric population. Furthermore, superior soft-tissue contrast of PET/MRI allows an accurate preoperative localization of the focal lesion detecting anatomical landmarks such as the bile duct, spleen, blood vessels. However, hybrid PET/MR imaging is not widely available being limited to a small number of pediatric centers.

Other PET tracers

^{68}Ga-peptide PET-CT: ^{18}F-DOPA PET/CT is currently included in HI diagnostic work-up when focal HI is suspected, representing the standard of care to distinguish between focal and diffuse forms of HI and to accurately localize focal forms [1]. However, ^{18}F-DOPA is not available in every country and its production technique is more difficult than other tracers. Food and Drug Administration (FDA) of the United

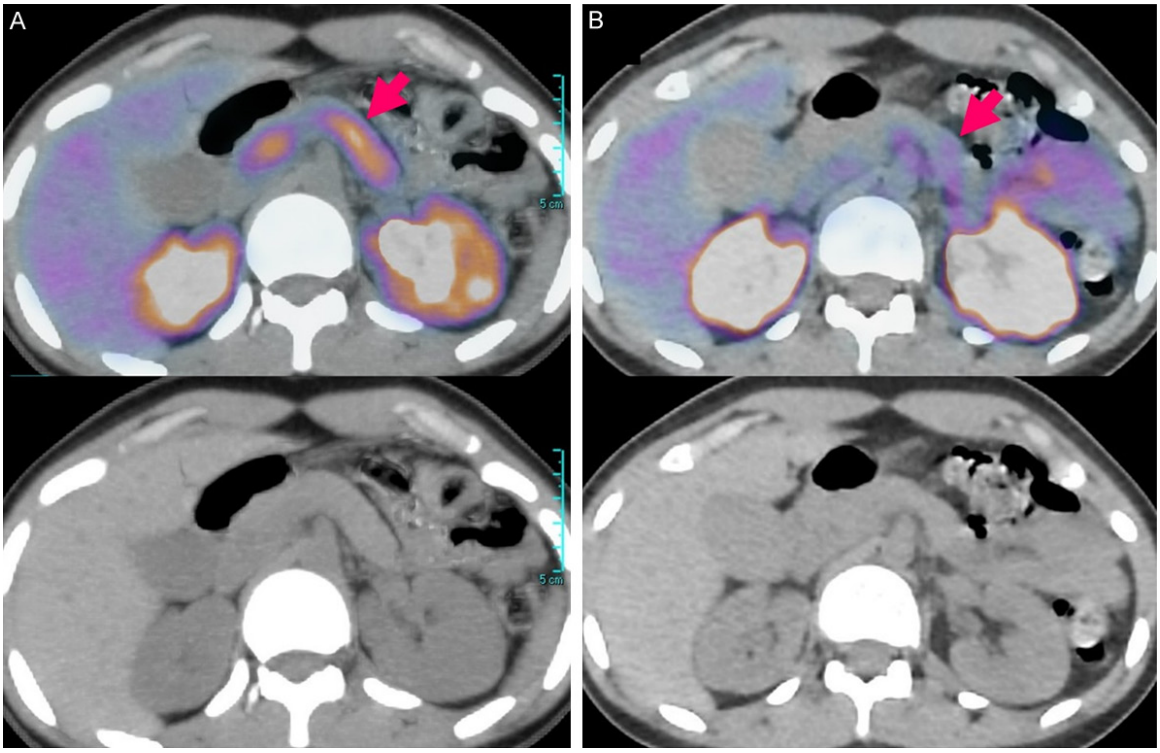

Figure 4. Factitious hyperinsulinism (Munchausen Syndrome by Proxy). Diagnosis of factitious hyperinsulinism could be a challenge with serious consequence related to repeated severe episodes of hypoglycemia (especially when misdiagnosed). Insulin/C-peptide ratio analysis is helpful in case of exogenous insulin injection, but it could not be discrepant in case of sulfonamide-induced factitious hypoglycemia. In this scenario, when antidiabetic agents are not identified by most common toxicological screening tests in urine and genetic test results are pending, PET-CT imaging could be used as prompt diagnostic tool integrating metabolic information provided by ^{18}F-DOPA and ^{68}Ga-DOTA peptide. **Figure 4** shows integrated dual-tracer PET/CT imaging performed in a case of severe hyperinsulinemic hypoglycemia, unresponsive to medical therapy with late age of onset (16 years), normal insulin/C-peptide ratio and no abnormal finding in urine drug testing. A. ^{18}F-DOPA PET imaging shows a diffuse ^{18}F-DOPA uptake throughout the pancreas without detection of ectopic focal lesion. B. ^{68}Ga-DOTATATE PET/CT imaging reveals a faint tracer uptake throughout the pancreas. PET-CT imaging ruled out the presence of pancreatic or ectopic lesions responsible for the hyperinsulinism (including focal HI or insulinoma). Due to the high clinical suspicious, other toxicological tests were performed detecting an antidiabetic drug in urine (glibenclamide).

States has not approved yet this tracer for routine clinical PET imaging studies in patients with hyperinsulinism (ClinicalTrials.gov Identifier: NCT00674440); in the US, F-DOPA gained FDA approval (October 10, 2019) for visualizing dopaminergic nerve terminals in the striatum for the evaluation of adult patients with suspected Parkinsonian syndromes.

Finding an alternative diagnostic option, some researchers investigated the use of ^{68}Gallium-labeled peptide (^{68}Ga-peptide) PET in patients with HI. PET imaging with ^{68}Ga-peptides (e.g., ^{68}Ga-DOTANOC [17] or ^{68}Ga-DOTATOC [38]) is based on radiolabeled somatostatin analogues with high affinity to the somatostatin receptor (SSTR), taken up by the endocrine cells of the islets of Langerhans expressing all SSTR subtypes.

The published works highlight that ^{68}Gallium peptide-PET is less sensitive compared to ^{18}F-DOPA PET with a high specificity in preoperative localization of the focal lesion [17, 38, 39]. Considering ^{68}Ga-peptide wider availability and its approval by FDA and EMEA (for evaluation and staging of neuroendocrine tumors), ^{68}Ga-peptide PET scan can be a reasonable and more accessible diagnostic tool for centers that do not have access to ^{18}F-DOPA PET/CT [38].

^{68}Ga-exendin PET-CT: ^{68}Ga-NODAGA-exendin-4 (Exendin PET) is a new promising tracer for the detection and localization of focal HI, which specifically binds to the GLP-1R expressed on pancreatic beta cells with high affinity (NCT03768518). As reported by Boss et al. [40] Exendin PET showed a higher diagnostic accu-

racy compared to standard ^{18}F-DOPA PET with a better image quality (higher contrast between uptake in the focal lesion and the rest of the pancreas) providing more unequivocal results. An easier detection of focal lesion allows a higher interobserver agreement between the readings, especially in the clinical non-expert setting, leading a major positive impact on the clinical management of HI patients. A tracer labeled with ^{68}Gallium (easily produced by a generator system without cyclotron facility) allows a wider availability representing another significant advantage.

The superior performance of Exendin PET needs to be confirmed by further investigations but it could be a reliable diagnostic tool to improve clinical management of HI patients.

Conclusion

Children affected by HI show a high incidence of neurodevelopment deficits due to continued metabolic instability. A prompt diagnosis is crucial to prevent a poor outcome searching an adequate treatment according to the HI subtype. Medical treatment is the first-line therapy but there are also some concerns about the safety profile of the drugs to treat HI due to the association with several adverse events. Diazoxide, for example, in addition to causing hypertrichosis as the most common side effect, has been associated to edema, pulmonary hypertension, neutropenia and thrombocytopenia [41]. Medical therapies side-effects and daily glucose level monitoring lead children to a stressful life with the constant risk of neurological damage secondary to uncontrolled hypoglycemic crisis. By identifying patients with focal HI, PET/CT allows selecting children who can benefit from the surgery, thus obtaining (in the hands of an experienced surgeon) a complete remission of the disease.

Knowledge, skills and multidisciplinary competence allow handling challenging cases, exploiting all the most accurate diagnostic tools (genetic analysis, molecular imaging enhanced by radiological information detected by CT) in the preoperative setting of HI lesions with the aim of increase the success rate of treatment.

In this regard, ^{18}F-DOPA PET/CT have radically changed life perspective of paediatric patients affected by focal HI transforming their quality of life and their future, not forgetting the significant impact on their families.

In the future new PET markers for diagnosis of focal HI are warrant, trying to combine an efficient tracer production with an optimal image quality to detect focal lesion for an adequate decision-making. Localization of the focus within the pancreas can be also improved by advanced 3D modelling and mapping techniques, for a more accurate planning of the selective partial pancreatectomy.

Disclosure of conflict of interest

None.

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