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EDITORIAL COMMENTARY

Could ^{68}Ga-somatostatin analogues be an important alternative to ^{18}F-DOPA PET/CT in pediatrics?

Arnoldo Piccardo[1] · Giorgio Treglia[2,3,4]

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A growing body of evidence supports the role of fluorine-18 dihydroxyphenylalanine (^{18}F–DOPA) PET/CT in different types of pediatric diseases [1–4]. Although, this radiotracer remains not largely available, its routine use is increasing in clinical practice, and it should be considered as an important diagnostic option in those Nuclear Medicine Departments highly specialized in pediatrics. The principal limitation of ^{18}F–DOPA is its high cost due to its not efficient production. Indeed, synthesis of ^{18}F–DOPA has generally been realized using an electrophilic approach. However, this electrophilic strategy produces only low amounts (0.6–2.6 GBq) of ^{18}F–DOPA even when using expensive production methods [5, 6].

One of the principal applications of ^{18}F–DOPA PET/CT in childhood, having relevant clinical implications in terms of disease management, is the detection and localization of focal form of congenital hyperinsulinism (CHI). CHI is an uncommon condition caused by an excess secretion capacity of insulin from islet β-cells. This condition represents the most common cause of persistent hypoglycaemia in infants and children [7] and, in the case of severe presentation, may be associated with loss of consciousness and even permanent brain damage. Therefore, early diagnosis and treatment of this disease is mandatory [8]. The surgical approach in the case of patient non-responders to dietary and medical treatment represents the therapy of choice especially if hyperinsulinemia is associated with focal pancreatic β-cells adenomatous hyperplasia (focal CHI) rather than with abnormal and diffuse insulin secretion (diffuse CHI). Indeed, focal CHI, after proper detection and localization, may be treated with a more conservative surgical approach consisting in selective resection. This approach may reduce the possibility of treatment-related events as diabetes or exocrine pancreas deficiency [8].

^{18}F–DOPA is a precursor of catecholamine and is taken up by the neuroendocrine cells by the pancreatic islet by using the large aminoacid transporter 2 [9]. Pancreatic neuroendocrine cells are able to take up amino acids and to transform them into biogenic amine by means of decarboxylation. The uptake mechanism of ^{18}F–DOPA by pancreatic neuroendocrine cells implies the detection of focal CHI by ^{18}F–DOPA PET/CT. Thus, ^{18}F–DOPA PET/CT represents a safe and non-invasive diagnostic option in CHI.

Indeed, in the present issue of the European Journal of Nuclear Medicine and Molecular Imaging, Christiansen and colleagues [10] deeply investigated the role of contrast enhanced (ce) ^{18}F–DOPA PET/CT in CHI and, at the same time, they interestingly compared the results with those of ce ^{68}Ga-DOTANOC PET/CT in the same setting. They evaluated 51 CHI patients by using ^{18}F–DOPA PET/CT or ^{68}Ga-DOTANOC PET/CT. Sixteen of these patients underwent both diagnostic modalities. The aim of the study was to validate the use of ^{68}Ga-DOTANOC as effective and widely available alternative to ^{18}F–DOPA in CHI. Although, somatostatin analogues (e.g., ^{68}Ga-DOTANOC) with high affinity to the somatostatin receptor (SSTR) subtypes 2, 3, and 5, should be taken up by the endocrine cells of the islets of Langerhans expressing all SSTR subtypes [11], only little information is available in the literature regarding the usefulness of radiolabelled somatostatin analogues in CHI [12, 13]. Indeed, this is the first and well-conducted comparison of such radiotracers in CHI. The authors underlined how an excess time spent before a proper management of severe

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✉ Arnoldo Piccardo
arnoldo.piccardo@galliera.it

[1] Department of Nuclear Medicine, E.O. Ospedali Galliera, Genoa, Italy

[2] Department of Nuclear Medicine and PET/CT Centre, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

[3] Health Technology Assessment Unit, General Directorate, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

[4] Department of Nuclear Medicine and Molecular Imaging, CHUV University Hospital, Lausanne, Switzerland

hypoglycaemia in CHI is an adverse prognostic factor for neurological impairment. In this field, the lack of a prompt availability of ^{18}F–DOPA may be overcome by using radiolabelled somatostatin analogues. The study confirmed, in a relatively high number of patients, the well-known [9, 14] high sensitivity, specificity, positive and negative predictive value (100%) of ^{18}F–DOPA PET/CT in detecting the focal form of CHI. Furthermore, the high accuracy of ^{18}F–DOPA PET/CT, confirmed by histopathology in the majority of the cases, was also achieved by combining functional PET information with the anatomical information provided by ceCT. In addition, the authors introduced a semi-quantitative analysis of ^{18}F–DOPA PET/CT results, and they found that 1.44 is the best SUVmax ratio cut-off able to identify focal CHI. On the other hand, the authors reported that ^{68}Ga-DOTANOC PET/CT had suboptimal sensitivity (78%) and negative predictive value (67%) in detecting focal CHI. In other words, the overall diagnostic performance of ^{68}Ga-DOTANOC PET/CT was significantly lower than that of ^{18}F–DOPA PET/CT. Thus, the authors conclude discouraging further use of ^{68}Ga-DOTANOC PET/CT in CHI.

This study confirmed that ^{18}F–DOPA is the tracer of choice in the assessment of one important diagnostic PET application in childhood (CHI). Nevertheless, the role of ^{68}Ga-somatostatin analogues seems to be promising in the evaluation of other pediatric diseases in which the role of ^{18}F–DOPA has already been evaluated. Brain tumors and neuroblastoma (NB) might be future applications of ^{68}Ga-somatostatin analogues in pediatric oncology. NB shows increased metabolism of catecholamines, but it may also overexpress somatostatin receptors, more precisely SSTR types 1 and 2 [15, 16]. Recent studies showed that both ^{18}F–DOPA and ^{68}Ga-somatostatin analogues are able to detect NB recurrence/metastases with high sensitivity [17–20]. In this context, the possible theranostic implications of ^{68}Ga-somatostatin analogues made these tracers of particular interest and more attractive than ^{18}F–DOPA. Indeed, preliminary data showed that peptide receptor radionuclide therapy seems to be safe, feasible, and associated with responses in patients with progression despite multimodality treatment [20].

Medulloblastoma is the most common of pediatric brain tumors [21] typically located in the posterior fossa. This tumor may be detected by ^{18}F–FDG [22] and the uptake seems to be associated with survival [23]. However, the principal limitation of the brain ^{18}F–FDG PET/CT, as in all brain tumors, is the high uptake of normal brain cortex limiting the delineation of cortical or pericortical tumors, even when dual-timepoint images are performed [24]. In this context, although characterized by very low normal cortical uptake, the sensitivity of aminoacid PET tracers, such as ^{18}F–DOPA, in detecting medulloblastoma seems to be low [25]. From this point of view, the reported high expression of somatostatin receptors, especially SSTR2 and 3 [26], in medulloblastoma open a door to the possibility of using ^{68}Ga-somatostatin analogues in disease assessment. Indeed, previous studies have shown that somatostatin receptor scintigraphy has a high diagnostic accuracy in children affected by Medulloblastoma [27, 28]. On the basis of these findings, ^{68}Ga-somatostatin-analogue PET/CT might play a potential role in the management of medulloblastoma and can be used to detect distant metastases and confirm the presence of residual/recurrent tumors. A potential advantage of ^{68}Ga-somatostatin-analogue PET/CT over the other PET tracers could be the selection of patients with medulloblastoma for SSTR-based radionuclide peptide therapy [29].

In the current era of a growing number of available PET tracers, pediatric imaging may benefit from the combined use of different metabolic and receptor-specific tracers. However, in children the selective and conscious use of the most appropriate PET tracers, based on the evidence and specific cost-effective analyses, is highly suggested in order to reduce futile radiation exposure.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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