Article published online: 2022-03-24

Case Report

Early diagnosis of focal congenital hyperinsulinism: A fluorine-18-labeled l-dihydroxyphenylalanine positron emission tomography/computed tomography study

ABSTRACT

Congenital hyperinsulinism (CHI) is responsible for hyperinsulinemic hypoglycemia which needs aggressive treatment in order to prevent neurological damages. Recent advances in genetics have linked CHI to mutations in many different genes that play a key role in regulating insulin secretion from pancreatic ß-cells. Furthermore, histopathological lesions, diffuse and focal, have been associated with these different genetic alterations. This short manuscript describes how the advent of fluorine-18-labeled L-dihydroxyphenylalanine-positron emission tomography/computed tomography (^{18}F-DOPA-PET/CT) scanning has changed the management of patients with CHI. ^{18}F-DOPA PET/CT imaging differentiates focal from diffuse disease and is 100% accurate in localizing the focal lesion. In these patients, the lesion can be surgically removed allowing complete resolution of clinical alterations. We report a case in which clinical experience together with rapid genetic analysis and imaging with ^{18}F-DOPA-PET/CT, were able to guide the correct clinical management of this condition. We confirm that advances in molecular genetics, imaging methods (^{18}F-DOPA PET-CT), medical therapy, and surgical approach have completely changed the management and improved the outcome of these children.

Keywords: Fluorine-18-labeled L-dihydroxyphenylalanine, focal congenital hyperinsulinism, hypoglycemia, pancreatectomy

INTRODUCTION

Congenital hyperinsulinism (CHI) is a rare but complex disorder caused by unregulated secretion from the beta-cells of the pancreas. Maintenance of euglycemia is necessary to minimize neurologic damages such as cerebral palsy, epilepsy, neurodevelopmental deficits, and even death. The term CHI refers to these inherited forms of hyperinsulinemic hypoglycemia (HH). CHI occurs due to mutations in key genes which play a role in insulin secretion from pancreatic β-cells. Currently, mutations have been identified in many different genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HK1, PGM1, PMM2, HNF4A,* and *HNF1A*) that lead to dysregulated secretion of insulin; the most common cause for CHI are mutations in the genes *ABCC8* and *KCNJ11* that encode the SUR1 and Kir6.2 subunits of the pancreatic β-cell K_{ATP} channel. Histologically, CHI is now classified into three groups: diffuse, focal, and atypical forms.[1-3] Focal forms are sporadic in inheritance and the lesions may occur in any part of the pancreas, although the tail and the body are the most common locations. The diffuse disease is due to recessive mutations in ABCC8 and KCNJ11 and affects the whole

Access this article online	
Website: www.wjnm.org	Quick Response Code
DOI: 10.4103/wjnm.wjnm_159_20	

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Submitted: 22-Dec-2020, **Revised:** 04-Apr-2021,
Accepted: 03-May-2021, **Published:** 01-Nov-2021

How to cite this article: Burroni L, Palucci A, Biscontini G, Cherubini V. Early diagnosis of focal congenital hyperinsulinism: A fluorine-18-labeled l-dihydroxyphenylalanine positron emission tomography/computed tomography study. World J Nucl Med 2021;20:395-7.

pancreas. The atypical form is related to an enlargement of β-cell nuclei, localized to discrete areas of the pancreas. The diffuse form is medically unresponsive and will require a near-total (>95%) pancreatectomy; the focal form, affecting only a small region of the pancreas, requires a limited pancreatectomy. Thus, the preoperative differentiation of these two subgroups is necessary.[4] However, the routine imaging techniques, such as US, computed tomography (CT), and/or magnetic resonance imaging (MRI), are unable in distinguishing the diffuse and focal forms of CHI. Nowadays, the imaging modality of choice to diagnose CHI is fluorine-18-labeled l-dihydroxyphenylalanine positron emission tomography/CT (^{18}FDOPA PET/CT) scan. The rationale of ^{18}F-DOPA PET/CT is based on the utilization of ^{18}F-DOPA as a precursor for dopamine. Pancreatic islets take up ^{18}F-DOPA and are able to convert it into dopamine using the enzyme DOPA decarboxylase. As part of the amine precursor uptake and decarboxylation system, normal islets in the pancreas also take up amine precursors (^{18}F-DOPA, for example) and decarboxylate them to amines by means of the aromatic amino acid decarboxylase enzyme. In hyperfunctioning islets (as in case of primary hyperinsulinemia), the uptake is more pronounced, and ^{18}F-DOPA PET/CT becomes of value for evaluating such patients. Because both forms of HH have an increased activity of this enzyme, the PET/CT scan usually demonstrates a uniform uptake of ^{18}FLDOPA throughout the pancreas in cases of diffuse CHI, whereas in focal CHI, the uptake is located only in particular foci of disease within the pancreas. Moreover, there have been reports of ectopic pancreatic tissue causing CHI in children. An ^{18}F-DOPA-PET/CT scan localized the ectopic lesions in the vicinity of the former head of the pancreas or in other districts.[1,4,5] For this reason, the preoperative evaluation of the focal lesions would have led to the removal of local and ectopic lesions and preservation of the rest of the pancreas.

CASE REPORT

An infant boy, born at 38 weeks' gestation via vaginal birth, body weight 4446 g (+3.01 SDS), length 52 cm (+1.1 SDS), head circumference 35 cm (+0.36 SDS), showed normal APGAR scores of 9 and 10 at 1 and 5 min, respectively. Due to the early detection of hypoglycemia, the infant was transferred to the neonatal intensive care unit, was on full enteral feeding, and received intravenous glucose treatment at a 1.2 g/kg/day dose to maintain blood glucose values within normal ranges. A panel of critical laboratory tests showed persistent high insulin levels (over 30 mcg/ml), negative ketonemia, low free fatty acid (213 mcmol/l, normal values 500–1600), normal insulin-like growth factor-1, cortisol, and ammonia levels in the setting of hypoglycemia, suggesting the diagnosis of CHI. Diazoxide treatment produced limited response, while subcutaneous octreotide allowed a significant decrease of intravenous glucose infusion. The diazoxide unresponsiveness suggested a potassium channel gene mutation. Therefore, genetic analysis and 18-F-DOPA PET/CT scan were organized. Genomic DNA was extracted from peripheral blood using the automated extractor Maxwell 16 (Promega). Sample enrichment and paired-end library preparation were performed using the commercial kit TruSight One (Illumina, San Diego, CA, USA), and sequencing was performed on NextSeq 500 instrument (Illumina, San Diego, CA, USA) with a flow cell high output, 300 cycles PE (150 × 2). Calling of variants was focused on genes for hyperinsulinism (ABCC8, GCK, GLUD1, HADH, HNF1A, HNF4A, INSR, KCNJ11, SCL16A1, and UCP2). Candidate variants were classified according to the ACMG-AMP criteria.[6] Identified variant was validated using Sanger Sequencing on AB3730 sequencer (Applied Biosystems), according to the manufacturers' protocols (primer and PCR conditions available on request). In the subject, we identified the mutation in the ABCC8 gene NM_000352.3:C.119T>G (p. Leu40Arg) previously described in a subject with CHI.[7] and demonstrated to prevent the export of the protein from the endoplasmic reticulum.[8] By performing segregation analysis, we demonstrated the paternal origin of the variant. The presence in the patient of a monoallelic recessive paternally transmitted ABCC8 mutation predisposes to somatic recessive condition by loss of heterozygosity and supports the diagnosis of focal CHI.

The patient received 4 MBq/kg of ^{18}F-DOPA intravenously. After 60 min, a whole-body scan was obtained in 3–4 bed positions. To obtain images for visual analysis, iterative reconstruction was performed and the reconstructed images were evaluated in a three-dimensional display using axial, coronal, and sagittal views to define pancreas. ^{18}F-DOPA PET/CT images showed intense ^{18}F-FDOPA uptake in the head of the pancreas, confirmed by a semi-quantitative evaluation (maximum standardized uptake value = 6.67) [Figure 1]. Due to the small size of the baby and the location of the lesion in the head of the pancreas, the first choice was diazoxide treatment which unfortunately was unable to control the decrease in blood glucose. As a second choice, octreotide treatment administered with an insulin pump was effective in keeping blood glucose levels within the normal range and allowing the child to grow normally. The growth of auxological parameters was very good during this treatment. At the age of 14 months, the baby underwent successful abdominal surgery with complete resolution of the hypoglycemia. On exploratory laparotomy, a solid focal lesion in the head of the pancreas was visible, with a diameter of 20 mm × 10 mm × 8 mm,

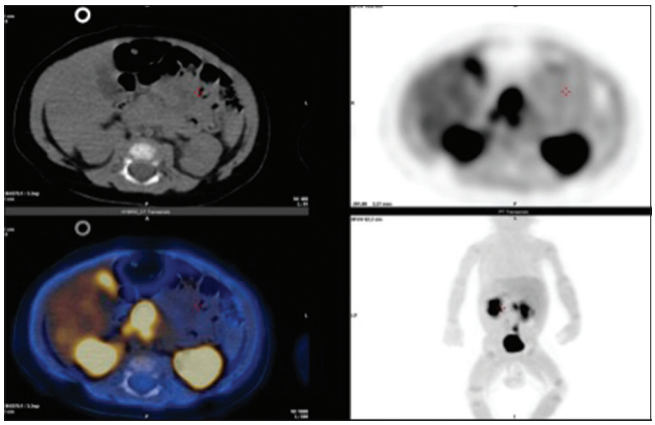

Figure 1: ^{18}F-fluoro-L-dihydroxyphenylalanine positron emission tomography/computed tomography scan images of focal congenital hyperinsulinism. Increased maximum standardized uptake value (6.67) confirms focal uptake of ^{18}F-fluoro-L-dihydroxyphenylalanine in the head of the pancreas

which was in close connection with the intestinal wall. It was excised easily including a small portion of intestinal tissue. Microscopically, the lesion contained hyperplastic islet cells separated by thin fibrovascular bands. The islets were adenoma like, and some of the β-cells within the lesion had enlarged nuclei typical of the focal form of CHI. Islets in the surrounding pancreas were normal.

DISCUSSION

At the time of surgery, the focal lesion was found exactly where the PET/CT position suggested and was removed with complete resolution of symptoms. Because focal lesions in many cases are difficult to identify during surgery and cannot be detected with conventional imaging approaches such as CT and MRI, ^{18}F-DOPA PET/CT scan is the preferred method of diagnosing CHI. Therefore, we confirm that ^{18}F-DOPA-PET/CT is a safe, noninvasive, and the investigation of choice in distinguishing between the focal and diffuse forms of CHI; the prompt and accurate localization permits the correct enucleation of the focal lesion preventing the risk of developing iatrogenic diabetes mellitus and pancreatic insufficiency.

Informed consent

According to the Italian Law, the parents of the patient signed a written informed consent for taking part in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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