THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2024.89021
Med Bull Sisli Etfal Hosp 2025;59(1):138–141

Case Report

Successful Management of an Infant with Congenital Focal Hyperinsulinism with No Apparent Lesion During Surgery

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Abstract

Congenital hyperinsulinism (HI) is the leading cause of persistent hypoglycemia in infants and children. Focal pancreatic lesions account for 30-40% of cases with congenital HI. With early diagnosis, these patients can be treated by resection of the lesion, making long-term medical care unnecessary. In this case, a 5-day-old newborn boy presented with convulsion due to severe and persistent hypoglycemia at his hospitalization in neonatal intensive care unit. Laboratory studies revealed very low levels of ketone bodies with inappropriately normal insulin levels during hypoglycemia. The patient was unresponsive to diazoxide treatment. The molecular genetic analysis revealed a heterozygous pathogenic variant in the ABCC8 gene. 18F-DOPA-PET/CT scan showed increased uptake of 18F-DOPA consistent with focal lesion at the tail of the pancreas. A focal pancreatectomy operation was performed when he was three months old. Histopathological evaluation confirmed focal endocrine cell hyperplasia. Hypoglycemia did not recur after the operation. CHI patients with ABCC8 / KCNJ11 mutation are not easy to manage with pharmacotheraphy. In the case of an identifiable focal lesion associated with CHI, surgery is the most preferred option. In focal CHI, as in our case, the lesion may not be visually evident and requires a surgeon experienced in CHI.

Keywords: ABCC8, focal, hyperinsulinism, KCNJ11, lesion, surgery

Please cite this article as "Misirli Ozdemir E, Akcay T, Akdag A, Karadag CA, Demir M, Tanik C, et al. Successful Management of an Infant with Congenital Focal Hyperinsulinism with No Apparent Lesion During Surgery. Med Bull Sisli Etfal Hosp 2025;59(1):138–141".

Congenital hyperinsulinism (CHI) is a heterogeneous disease caused by defects in regulating insulin secretion. It can potentially lead to permanent neurological damage, prompt diagnosis and appropriate management are important.[1,2]

There are three histological forms of CHI; focal form (F-CHI), diffuse form (D-CHI), and atypical. These are clinically indistinguishable but differ at least partially in the type of genetic defect.[3] F-CHI is caused by a heterozygous ABCC8 or KCNJ11 gene mutation inherited paternally along with somatic loss of the 11p15 region of the maternal chromosome and encompasses 30-40% of cases with CHI.[4]

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Submitted Date: May 09, 2024 **Revised Date:** July 10, 2024 **Accepted Date:** July 18, 2024 **Available Online Date:** March 18, 2025

The best way to distinguish focal forms from diffuse ones of CHI is to perform Fluorine-18 L-3, 4 dihydroxyphenylalanines positron emission tomography-computed tomography (18F- DOPA-PET/CT) scan. In cases of F-CHI, surgical removal of the affected tissue is usually curative.[5,6]

Herein, we report the successful treatment of a case with F-CHI to underpin the importance of molecular genetics in identifying patients with CHI who may be cured via resection of the focal lesion.

Case Report

A term newborn male, born to nonconsanguineous parents with a birth weight of 3160 g (-0.5 SD) developed convulsion due to severe and persistent hypoglycemia on the fifth day of his hospitalization in the neonatal intensive care unit (NICU) due to transient tachypnea of the newborn. There was no history of maternal diabetes. Continuous infusion of glucose with 8-10 mg/ kg/minute rate was started and diazoxide was added (titrated to 20 mg/kg/day) to maintain normoglycemia.

Laboratory workup revealed inappropriately low serum levels of ketone bodies (beta-hydroxybutyrate: 0.16 mmol/L [normal: >1.8 mmol/L]) in the presence of low plasma glucose levels (44 mg/dL) and inappropriately normal insulin levels (3.7 µU/mL [normal: 2.6-24.9 µU/mL]).

Despite glucose infusion and diazoxide treatment, hypoglycemic episodes persisted on DOL (day of life) 18 and were diagnosed as being diazoxide resistant and diazoxide was stopped. Then octreotide has been started (10 µg/kg/day). With octreotide treatment and feeding 3 hourly, blood sugar measurements were in normal range on DOL 45. Echocardiography and electrocardiography were performed to screen for cardiac pathologies. Both were normal in our case. In the second month of follow-up, lanreotide (10 mg given every 4 weeks by subcutaneous injections), a long-acting form of treatment, was started for normoglycemia maintenance. Molecular genetic testing revealed a previously reported heterozygous paternally inherited pathogenic ABCC8 variant (p.Gly52Glufs*26, c.155del), and subsequently, the 18F-DOPA-PET/CT scan confirmed increased uptake of 18F-DOPA, consistent with a focal lesion at the tail of the pancreas (Fig. 1).

Surgery was performed on DOL90 by a team of experienced surgeons. The focal lesion detected with nuclear imaging was not identified by inspection and palpation of the pancreas.

Distal pancreatectomy was performed and 1 cm caudal to the tail of the pancreas was empirically removed, including the region where the lesion was shown radiologically. The surgical procedure was terminated upon confirmation of clean surgical margins in the intraoperative frozen section analysis.

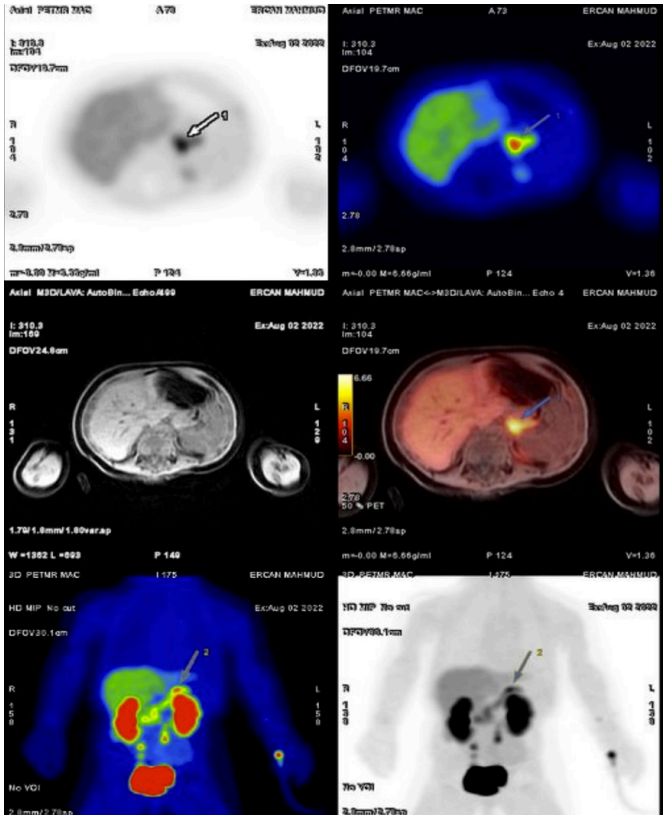

Figure 1. 18F-DOPA-PET/CT scan of a focal lesion in the tail of the pancreas.

The histopathologic examination confirmed focal endocrine cell hyperplasia (Figs. 2, 3). Postoperatively, maintenance of normoglycemia during an 8-hour fasting confirmed surgical cure. During the six-month follow-up hypoglycemia did not recur. Normal somatic development and normoglycemia were achieved without any medication or dietary intervention.

Discussion

Herein, we present a case of F-CHI that is successfully treated via partial pancreatectomy. This case confirms the need for genetic tests for CHI to choose the best treatment options.[7]

In the current case, diazoxide was administered at 15 mcg/kg/day for 5 days, but there was no 25% decrease in GPH, suggesting diazoxide resistance.[3] Hence, treatment was switched to octreotide with the attainment of normoglycemia.

Lanreotide is a recently approved agent in the treatment of CHI[8] and is often preferred over its short-acting counterpart due to its dosing schedule. In our case, a single dose

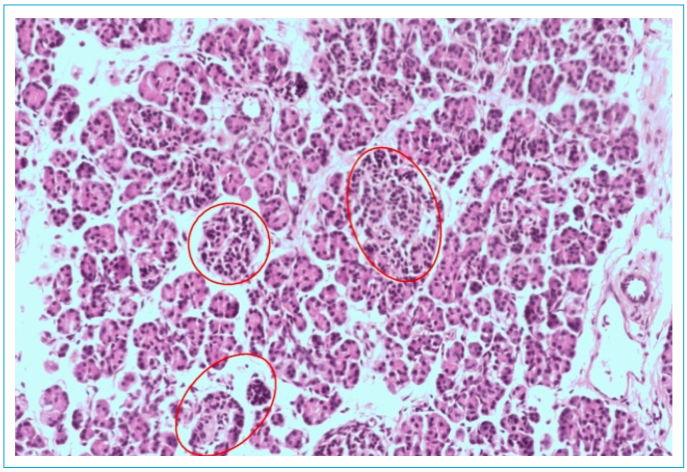

Figure 2. Hematoxylin eosin staining at 200 magnification. Localized cell islands (marked areas), increased in number and irregularly distributed within the tubuloglobular structures within the pan-creas.

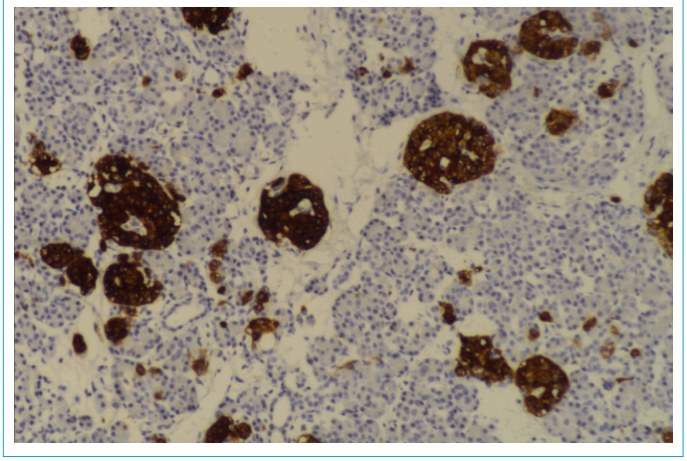

Figure 3. Synaptophysin staining at 200 magnification. Increased number of islets and isolated neuroendocrine cell group in pancreatic section.

of 10 mg of lanreotide was enough to maintain normoglycemia for approximately 45 days. The long-acting form of octreotide should be used with caution in cases younger than two years.[9] Yet, we did not experience any lanreotide-related side effects with a single use at a dose of 10 mg/month.

Congenital hyperinsulinemia can be associated with hypertrophic cardiomyopathy or dysrhythmia. Bulbul et al.[10] reported severe left ventricular hypertrophy, subaortic stenosis, mitral regurgitation and dysrhythmia, in a case with CHI. However, cardiac abnormalities were not detected in our case.

Molecular genetic analysis has a pivotal role in diagnosis and potentially guiding the definitive treatment. Most of the biallelic ABCC8 mutations are diazoxide unresponsive; however, the response of monoallelic mutations to diazoxide is variable. Patients who do not respond to medical treatment undergo neartotal pancreatectomy or focal surgery depending on the molecular genetics work-up and subsequent imaging if indicated.[11] Our case presented with a paternally inherited heterozygous pathogenic ABCC8 frameshift variant. Monoallelic paternally transmitted ATP-sensitive potassium (KATP) channel gene mutations predict focal hyperinsulinism with 97% sensitivity and 90% specificity.[12]

Focal CHI cases harboring ABCC8/KCNJ11 pathogenic variants are more difficult to manage through pharmacotherapy.[4,13] In the case of an identifiable focal lesion associated with CHI, surgery is the most preferred option. Focal lesions can be localized with 18F-DOPA-PET scan-ning. Complete excision of the lesion is confirmed histologically.[14] In the era before molecular genetic testing, near-total pancreatectomy (95-98%) was the common option to provide cure or facilitate medical management, although with postoperative diabetes in 20% of the cases and variable success rates in the maintenance of normoglycemia.[15,16]

In F-CHI, as in our case, the lesion may be deeply located and not visually evident. In this case, to avoid total pancreatectomy, the estimated suspicious area is removed based on preoperative molecular diagnosis and 18F-DOPA-PET/CT scan results. Intraoperative biopsy was performed and surgical cure was demonstrated via frozen section analysis revealing clear margins on histopathological examination. Therefore, the operative management of a F-CHI requires experienced pathologists as well as surgeons since the lesion evident on nuclear scanning may not always be evident during the operation.[16]

In conclusion, the presented case confirms the significance of molecular genetic testing in patients with CHI to guide appropriate management. The presence of increased focal uptake in functional imaging does not always secure the anatomic location of the lesion. This case report highlights the need for an experienced surgeon in the management of F-CHI since, in some instances, the tumoral mass may not be visible in the intraoperative room.

Disclosures

Informed Consent: The authors declared that the patient was informed and approved about this information.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.M.O.; Design – E.M.O.; Supervision – A.D.C., A.U.; Materials – T.A., C.T., A.A.; Data collection &/ or processing – E.M.O., M.D., C.A.K.; Analy-sis and/or interpretation – E.M.O.; Literature search – E.M.O.; Writing – E.M.O., A.U.; Critical review – A.D.C., A.U.

Use of AI for Writing Assistance: The authors declared that artificial intelligence (AI)-enabled technologies (such as Large Language Models [LLMs], chatbots or image generators, ChatGPT) were not used in the study.

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