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Case Report

Successful treatment of a newborn with congenital hyperinsulinism having a novel heterozygous mutation in the *ABCC8* gene using subtotal pancreatectomy

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ABSTRACT

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in newborns and infants. CHI is characterized by unregulated secretion of insulin from pancreatic β cells. Here, we reported the case of a large-for-gestational-age, full-term newborn that suffered from CHI and developed severe and persistent hypoglycemia at an early stage of life. The infant was nearly unresponsive to medical treatment, which included continuous intravenous glucagon infusion, oral diazoxide, and nifedipine. After medical treatment had failed, an 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography scan of the patient showed a focal lesion at the neck of the pancreas. The patient received subtotal pancreatectomy, and shortly after the procedure, the patient's blood sugar returned to the normal range. The patient was confirmed to have a novel heterozygous mutation at position c.2475+1G>A of the *ABCC8* gene. This is the first report of a focal form of CHI in a patient in Taiwan, which had preoperatively been confirmed using 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography.

1. Introduction

Congenital hyperinsulinism (CHI) is a genetic disorder with clinical symptoms that can range from mild to severe hypoglycemia. This disease is also the major cause of persistent hypoglycemia among newborns and infants [1]. In the literature, nine genes have been reported to be associated with CHI, with the most common genetic causes of CHI being mutations in either *ABCC8* or *KCNJ11* [2]. Both genes are located on chromosome 11p; they encode, respectively, the sulfonylurea receptor 1 (SUR1) and Kir 6.2, both of which are subunits of the adenosine triphosphate-sensitive potassium channel (K_{ATP} channel) found in the pancreatic β cells. Most patients with either an *ABCC8* mutation or a *KCNJ11* mutation have been found to be unresponsive to diazoxide, which is the first-line treatment for CHI [3]. In the past, those who were unresponsive to medical therapy needed to receive a near-total pancreatectomy in order to treat their severe and refractory hypoglycemia. However, remarkable progress has been made regarding the diagnosis of CHI, which has included the use of molecular diagnostic approaches and 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) scanning; these procedures help distinguish between the focal and diffuse forms of CHI. The information obtained from these aids in deciding an optimal management strategy for a given patient and helps predict the outcome [4]. Additionally, the incidence rate of the focal form of CHI has been reported to be higher in Asians, which makes such progress especially important for the treatment of Asian populations [5,6]. Here, we report the case of a Taiwanese newborn with CHI who was

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found to have a genetic mutation within the *ABCC8* gene; this is the first report in the literature of this mutation. The ^{18}F-DOPA PET scan diagnosed the patient as having a focal disease and accurately localized the lesion at the neck of the pancreas. The patient's blood sugar returned to the normal range after subtotal pancreatectomy. The patient, who is now being followed up at our outpatient department, has been found to be euglycemic and is fulfilling normal developmental milestones.

2. Case report

This case describes a Taiwanese male patient who was born to a nondiabetic G1P1 mother at 38 weeks of gestational age by vaginal delivery and had a birth weight of 3660 g (> 90th percentile); the baby had Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. During hospitalization, hypoglycemia (37 mg/dL) was detected on the 2nd day of life, and a high glucose infusion rate was required to keep his blood glucose in the normal range. Despite continuous intravenous glucose supplementation and oral feeding, his blood sugar levels still fluctuated from 21 mg/dL to 145 mg/dL. Two episodes of seizure occurred during his 3rd day of life while the patient was hypoglycemic (40 mg/dL and 37 mg/dL). At this point, the patient was treated with intramuscular phenobarbital.

An endocrine survey during hypoglycemia (serum blood glucose, 39 mg/dL) showed a normal thyroid hormone level (free T4, 1.27 ng/dL), a normal growth hormone level (10.5 ng/mL), and a normal cortisol level (11.75 μg/dL), and the patient's blood was negative for ketones. However, an inappropriately elevated serum insulin level of 29.9 μIU/mL (normal range, 3–16 μIU/mL), an abnormal c-peptide level of 4.62 ng/mL (normal range, 1–1.5 ng/mL), an abnormal ammonia level of 104 μg/dL (normal range, 19–60 μg/dL), and a high insulin/glucose ratio of 0.77 (> 0.4) were noted. Treatment with diazoxide was tried on the 40th day of life, and the drug was gradually increased over the following days until the maximum allowable dose of 20 mg/kg/d was reached. During this period, intermittent hypoglycemia episodes were still noted, especially when we tried to taper off the intravenous glucose infusion. Nifedipine, together with a continuous glucagon infusion, was then started on the 52nd day of life, but again no clinical improvement was observed. Since the patient was unresponsive to all available medical treatments, surgical intervention was then planned in order to treat the patient's refractory hypoglycemia.

Prior to the operation, we arranged for an ^{18}F-DOPA PET scan. This resulted in the detection of a focal lesion at the neck of the pancreas (Fig. 1). Based on this finding, the patient received a subtotal pancreatectomy on the 83rd day of life, and during surgery a nodule-like lesion of about 1 cm × 1 cm was identified at the neck of the pancreas and removed; this nodule was compatible with the lesion found on the PET scan (Fig. 2). After the operation, the patient's blood sugar level returned to the normal range, and we were able to successfully discontinue intravenous treatment of the patient on the 93rd day of life. The patient was then discharged on the 95th day of life and has been followed up at our outpatient department; he is euglycemic and has reached his normal developmental milestones.

2.1. Detection of mutations in the ABCC8 gene

Genomic DNA was isolated from the buffy coat of the whole blood of this patient using standard procedures. All exons and intron/exon boundaries of the ABCC8 gene was amplified by gene-specific primers. The PCR product was purified using the ExoSAP-IT PCR cleanup reagent (USB). The amplicons used the fluorescence-labeled method with an automatic sequencer (model 3730; Applied Biosystems) to verify the nucleotide sequence (TaqDyeDeoxy Terminator Cycle Sequencing kit). The variations were analyzed using the reference sequences from GenBank (NM000525.3 and NM000352.4).

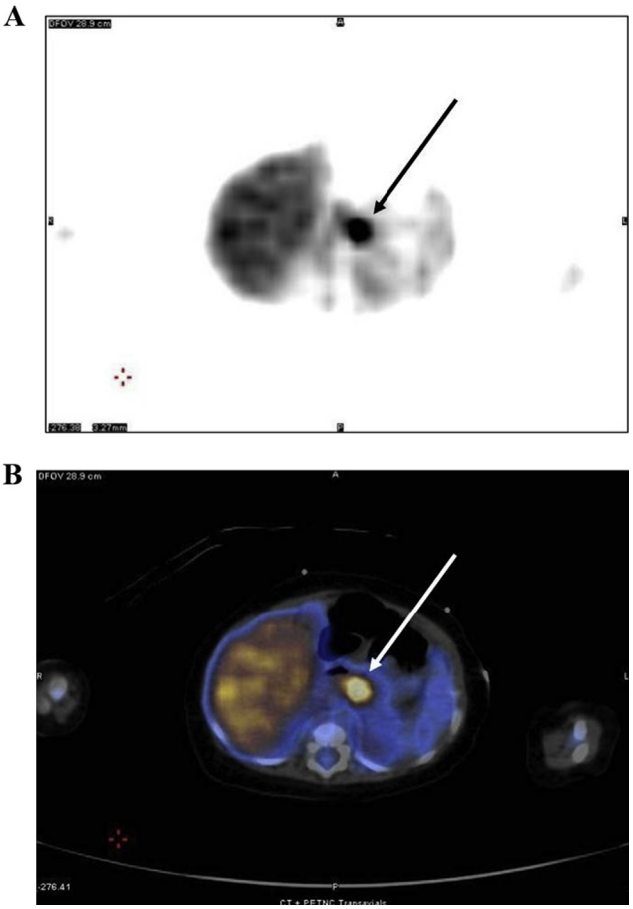

Fig. 1. (A) Transverse view of a maximum intensity projection ^{18}F-DOPA PET image that demonstrates a focal lesion at the neck of the pancreas (black arrow). (B) Transverse view of the abdominal computed tomography + PET that revealed a bright enhancement near the neck of the pancreas (white arrow). ^{18}F-DOPA PET = 18-fluoro L-3,4-dihydroxyphenylalanine positron emission tomography; PET = positron emission tomography.

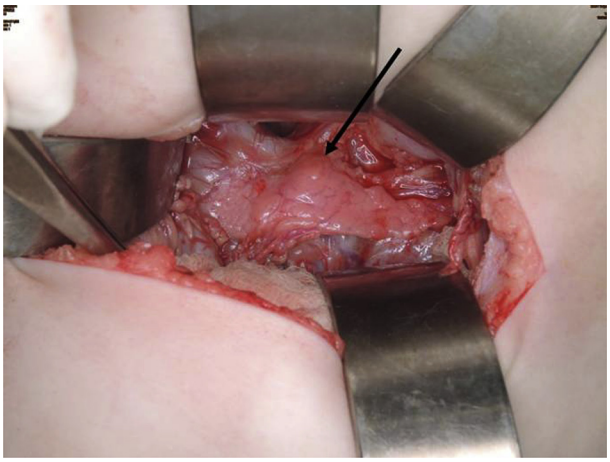

Fig. 2. A white nodule (1 × 1 cm^2) found at the neck of the pancreas during the operation.

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