Successful Treatment of Congenital Hyperinsulinism Due to *KJNJ11* Gene Mutation with Long-Acting Release Octreotide: A Case Report from the Arab Region

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J Diabetes Endocrine Practice 2023;6:33–36.

Abstract

Congenital hyperinsulinism is a rare hereditary condition that is caused by various gene mutations related to the function of the pancreatic β-cells. It is characterized by dysregulation of insulin secretion leading to profound and recurrent hypoglycemia. Its clinical presentation, histology, response to treatment, and underlying genetic defects are variable making it a heterogeneous condition. Pancreatectomy is indicated in diazoxide un-responsive cases. However, surgical treatment is associated with the possibility of persistent hypoglycemia and iatrogenic diabetes. We report a 3 months old girl who presented with hyperinsulinemic hypoglycemia. She was born to consanguineous parents and had a history of four neonatal deaths in siblings. Whole exome sequencing detected a *KCNJ11* variant c.350_352del p.(Phe117del) in a homozygous state. Pancreatic scan (positron emission tomography/computed tomography) showed a diffusely increased radioisotope uptake in the head and tail of the pancreas. She was resistant to diazoxide and nifedipine and was shifted to octreotide treatment through multiple daily subcutaneous injections initially. Treatment was changed to monthly depot injection of octreotide that resulted in euglycemia. She kept a normal rate of growth, insulin-like growth factor-1, and liver function. This case is an example of an alternative effective medical therapy that avoids major surgical intervention and prevents long-term complication of recurrent hypoglycemia and iatrogenic diabetes resulting after surgery.

Keywords

- congenital hyperinsulinism
- KCNJ11
- hypoglycemia
- octreotide

DOI https://doi.org/10.1055/s-0043-1764457.
ISSN 2772-7653.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Congenital hyperinsulinism (CH) or persistent hyperinsulinemic hypoglycemia of infancy is a rare hereditary condition that is caused by various gene mutations related to the function of the pancreatic β-cells. It is characterized by dysregulation of insulin secretion leading to profound and recurrent hypoglycemia. Clinically, nonketotic hypoglycemia is its most common presentation.[1]

CH is known to be the main cause of recurrent and persistent hypoglycemia in infancy. Its incidence is variable but ranges from 1/27,000 to 1/50,000 in newborns.[2] The condition was first described in 1938 and was called "Nesidioblastosis." It is known to be a heterogeneous condition in multiple aspects including clinical presentation, histology, underlying genetic etiology, and response to treatment.[3] It is an inherited condition with the most common form of inheritance being autosomal recessive but can also be inherited in an autosomal dominant pattern.[1] Histologically, it can be of either diffuse or focal type. The diffuse type is more commonly caused by recessive mutations in *ABCC8/KCNJ11* kATP channel genes. However, it can also be transmitted in an autosomal dominant fashion. In focal disease, there is an inherited *ABCC8/KCNJ11* mutation that is paternally transmitted. In this form, there is a somatic loss of heterozygosity for the allele 11p.[3] Mutations in *ABCC8* and *KCNJ11* genes are the most common cause of the disease. *KCNJ11* gene is a much smaller gene compared with *ABCC8 and f*ewer loss-of-function mutations have been reported in it.[4] Both dominant and recessive ABCC8 and *KCNJ11* mutations have been reported.[5]

After failure of medical treatment, pancreatectomy is recommended in diffuse form and near-total pancreatectomy is often performed. However, the incidence of persistent hypoglycemia remains high after surgery. Furthermore, iatrogenic diabetes is commonly seen post-surgery.[6] In one report, over 96% of patients who underwent subtotal pancreatectomy presented with diabetes after 11 years.[7] Long-term, continuous, subcutaneous (SC) octreotide infusion can be used successfully to treat hyperinsulinemic hypoglycemia due to kATP channel mutations. It provides an alternative to surgery to affected patients.[8] Long-acting release (LAR) octreotide has also been used on monthly basis primarily to avoid the inconvenience of multiple daily injection or the continuous infusion using pumps.[9,10]

CH remains a serious condition that requires rapid diagnosis and treatment initiation. Hence, early diagnosis and rapid initiation of appropriate treatment are critical to prevent any neurological adverse effect of hypoglycemia. There is still no known cure for the condition and surgical treatment results in long-term adverse effect. Improved medications are still required to provide ideal treatment for the condition.

Case Presentation

The patient is a 3 months old girl. She was referred from a district hospital for the management of refractory hypoglycemia. She presented with bradypnea, lethargy, floppiness, and recurrent seizures from the age of 3 days. The referring hospital documented severe symptomatic hypoglycemia. Investigations confirmed a nonketotic hypoglycemia. She was born by normal vaginal delivery at term. Her birth weight was 3.7 kg. Her parents are first-degree cousins. Mother gave history of a still born and four neonatal deaths. Subtle dysmorphic features were noted in the patient. She had delayed motor developmental milestones as she was not able to support her head at the age of 3 months.

Critical blood sample at an episode of hypoglycemia (blood glucose of 34 mg/L) showed a high level of insulin of 7.07 mU/L and a c-peptide of 3.11 ng/mL. Blood and urine ketones were negative. She had a normal serum cortisol, growth hormone, ammonia, lactate, liver function test, serum albumin, acylcarnitine profile, and fatty acid screen. Her amino acid and organic acid screens were normal.

She required a high concentration of dextrose with a glucose infusion rate of 16 mg/kg/min.

She was unresponsive to diazoxide that was tried at the maximum dose by the referring hospital for 2 weeks along with continuous enteral feed through gastrostomy and parenteral dextrose. Addition of nifedipine did not result in improving the hypoglycemia. Injection of glucagon in one of hypoglycemia episodes resulted in a rapid increase in glucose level.

She had a Pancreatic Scan (positron emission tomography/computed tomography [PET/CT]) with Ca-68-DOTATATE (Gallium-68 DOTATATE) at a dose of 0.5 mCi. The scan showed a diffusely increased radioisotope uptake in the head and tail (maximum standardized uptake value: 7.8 and 8.5) for the head and tail respectively. There was a relative sparing of the body of the pancreas (►**Fig. 1**). No evidence of focal DOTATATE uptake within the pancreas. There is a physiologic tracer activity in the liver, spleen, adrenals and kidneys. There is no DOTATATE-avid mesenteric, retroperitoneal, pelvic or inguinal lymphadenopathy (►**Fig. 2**). She had a normal echocardiography and normal brain magnetic resonance imaging scan.

Whole exome sequencing detected the *KCNJ11* variant c.350_352del p.(Phe117del) in a homozygous state.

She was started intravenous infusion of octreotide with a maximum dose of 0.6 µg/kg/h at which she achieved normoglycemia. After 2 weeks, she was shifted to SC injections at a dose of 35 µg every 6 hours. LAR octreotide intramuscular injection (depot octreotide) was added monthly and the SC octreotide gradually stopped. The patient was continued initially on gastrostomy feed with Maxijul supplement with close monitoring of glucose profile. Gradually, she started to feed normally with maintained glycemia. Her growth parameters were normal for age and continued to have normal liver transaminases and insulin-like growth factor-1. She had no further reported hypoglycemia while on the depot monthly injection.

Discussion

Persistent hypoglycemia caused by CH may have negative consequences on neurological development. Early diagnosis

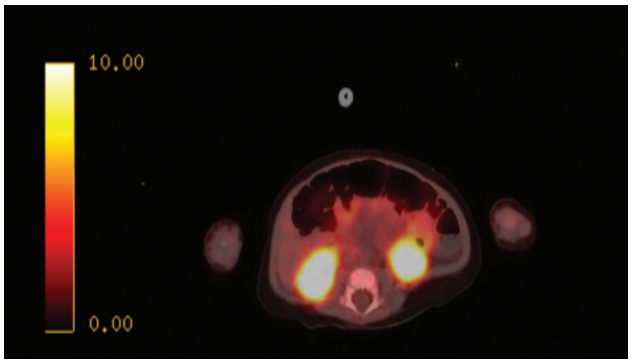

Fig. 1 A coronal section showing a diffuse increase in the radioisotop DOTATATE uptake in the head and tail of the pancreas with relative sparing of the body of the pancreas. No evidence of focal uptake within the pancreas. Radioisotop uptake is indicated in standardized uptake value scale from 0.00 to 10.00.

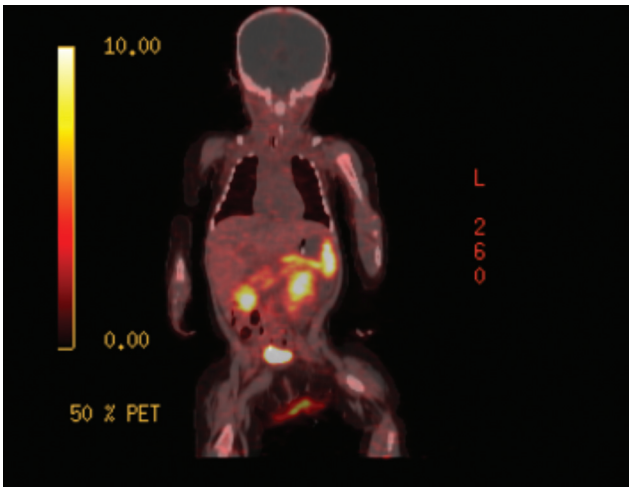

Fig. 2 A sagittal section of body showing uptake of radioisotop DOTATATE showing a physiologic tracer activity in the liver, spleen, adrenals, and kidneys. There is no DOTATATE uptake in mesenteric, retroperitoneal, pelvic, or inguinal lymphadenopathy.

and proper rapid treatment are critical in restoring the ability of ketone bodies production as an alternative energy requirement for the brain.

Over the past decades, there has been significant advances in both diagnosis and treatment of CH. These advances led to the reduction in the long-term complications of the psychomotor delay related to hypoglycemia. The improvement was made possible by the advances in molecular genetic diagnosis and the radiological detection of the pancreatic lesions. The main known genetic etiologies currently are inactivating mutations of the kATP channel genes (*ABCC8* and *KCNJ11*), *HADH*, *HNF1A HNF4A*, and *UCP2* or activating mutations of *GLUD1*, *SLC16A1*, and *GCK*.[11] Genetic alteration has been identified in 50% of patients involving nine genes related to insulin secretion.[12]

Our patient had an in-frame deletion that causes the loss of residue Phe at position 117. This variant has been previously described in the literature in homozygosity and compound heterozygosity in patients with CH.[1] One of the reported mutations resulted in deletion of phenylalanine at codon 117 (p.Phe117del, F117del). Clinically, the patient presented with hypoglycemia at the first week of life, was unresponsive to diazoxide, and required pancreatectomy.[1]

In addition to prediction of the histological type through genetic testing, radioisotop imaging PET/CT can also be used to indicate the type and extent of the anatomical abnormality. Confirmed focal disease through 18F-DOPA-PET-CT scan is an indication for surgery. The scan helps guiding surgeons for the exact location of the focal lesion. In this circumstance, the treatment of choice is partial pancreatectomy aiming at removal of the lesion. Surgery is also indicated in diffuse type unresponsive to diazoxide in which a near-total pancreatectomy is indicated. Pancreatectomy carries a high risk of persistent hypoglycemia. exocrine pancreatic insufficiency, and also development of diabetes mellitus later in life.[7] Our patient had a diffuse increase of the radioisotop DOTATATE uptake in the head and tail of the pancreas with relative sparing of the body of the pancreas. She had no evidence of focal uptake within the pancreas (►**Fig. 1**).

Octreotide is a long-acting somatostatin analog. It acts on somatostatin receptor 2. It activates the kATP channel on the β-cells leading to hyperpolarization of the cell membrane. This leads to inhibition of the voltage-gated calcium channel and suppression of insulin secretion. Octreotide also acts on the signal transduction pathway cyclic adenosine monophosphate production inhibition.[13] Continuous SC octreotide infusion is known to be a feasible alternative to surgery in patients with diazoxide-unresponsive kATP channel mutation.[8] In a single-arm, open-label clinical trial (SCORCH study), octreotide injection was effective as a treatment for CH. In this trial, 19 diazoxide-unresponsive patients were treated by multiple daily injections or continuous infusion of SC octreotide. The treatment was well tolerated and effective in the majority of patients.[14] The clinical outcome was reported by Demirbilek et al in 28 patients (25 with mutations in the kATP-channel genes). The patients were treated with multiple daily octreotide injection of 5 to 30 µg/kg/day for a mean period of 52.4 months. Therapy was effective in avoiding surgery in 42.8% of patients and they had was no evidence of growth deceleration.[15]

A major drawback in its use in this form is the need of multiple daily injections. Multiple studies have been conducted on LAR somatostatin analogues. The aim was to explore the effectiveness on disease control and to study the quality of life of patients and parents.[9,16–18] Le Quan Sang et al reported successful treatment with LAR octreotide for 10 diazoxide unresponsive patients and 5 patients with ABCC8 gene mutation.[9] van der Steen study described successful treatment with LAR octreotide in 24 out of 27 patients, and 13 of those had ABCC8 and 3KCNJ1 mutations.[17] Corda et al had similar successful results on using LAR octreotide in four patients of whom two had ABCC8 mutations.[18] From the Arab region, Al Anezi et al reported a successful experience with the use of LAR octreotide in a child who is homozygous for ABCC8 missense mutation, p. Ala390Glu.[10]

Conclusion

CH remains an important cause of morbidity in neonates and children particularly in consanguineous families. Long-acting octreotide can be an effective modality of treatment in the diffuse type of the disease. It enables easier treatment of a monthly injection rather than continuous or multiple daily injection of short-acting octreotide and avoids invasive surgical treatment with pancreatectomy and its complex sequalae.

What is already known on this topic?

Hypoglycemia resulting from kATP channel mutation can be due to focal or diffuse disease. Diazoxide unresponsive causes can be severe enough to require pancreatectomy. Surgery is known to be associated with persistent hypoglycemia and iatrogenic secondary diabetes.

What does this study adds?

Severe hypoglycemia caused by congenital hyperinsulinism due to KCJN11 mutation in kATP channel can be safely and effectively treated with the long-release monthly octreotide. This approach offers an alternative medical treatment to invasive surgery.

Author Contributions

G.M.H. and A.Al-H. are the intensive care consultants under whom the patient was attended. They followed the patient up and provided detailed information on her progress. M.E. wrote a draft for the manuscript and provided the figures. I.S. is the surgeon who was involved in her care and led discussion over surgical treatment. A.D. advised on the medical treatment, wrote the final manuscript, liaised between authors, and submitted the article. All coauthors reviewed the submitted manuscript.

Conflict of Interest

None declared.

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