

Outcome of eight patients with congenital hyperinsulinism (CHI) studied with [18F]Dihydroxyphenyl-Alanine Positron Emission Tomography Imaging (18F-DOPA-PET-CT) in

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INTRODUCTION Congenital hyperinsulinism (CHI) results from inappropriate insulin secretion during hypoglycaemia. The most commonly found mutations are in *ABCC8* and *KCNJ11* which encode for the pancreatic β -cells ATP-sensitive-potassium channel (KATP) subunits SUR1 and KIR6.2. Inactivating mutations in these genes cause channel closure or complete loss of the channel resulting in membrane depolarization and unregulated insulin release.

Diagnosis of CHI is based on the presence of detectable plasma insulin during hypoglycaemia, suppressed β -hydroxybutyrate and NEFA and inappropriate response to glucagon (increase of glucose level > 30 mg/dl). Diazoxide binds to SUR1 causing the channel to open, patients with functionally severe KATP channel mutations fail to respond to this treatment. Octreotide and sirolimus have been used in some cases. Focal and diffuse pancreatic disease can be differentiated by 18F-DOPA-PET-CT scanning. In the former a lesionectomy can resolve hyperinsulinism whereas diffuse disease often requires extensive pancreatectomies. Diffuse disease is generally caused by the recessive inheritance or two KATP channel mutations whilst focal disease develops when an individual inherits a single recessively-acting KATP channel mutation on the paternal chromosome which is unmasked by paternal uniparental disomy within the pancreas. Monoallelic recessively-acting *ABCC8*/*KCNJ11* mutations predict focal disease with 69-97% sensitivity.

OBJECTIVE: To report a retrospective series of 8 patients from four pediatric hospitals in Argentina with CHI, describing clinical outcome, laboratory, genetic and 18F-DOPA-PET-CT findings.

MATERIALS AND METHODS: Diagnosis of CHI was made in the presence of: Glucose <50mg/dl (2.8mmol/l), with detectable plasma insulin. Transient and syndromic forms were excluded. Age, laboratory results during hypoglycemia, response to treatment, side effects of medical treatment, *ABCC8*/*KCNJ11* sequencing and 18F-DOPA-PET-CT were recorded. Response to diazoxide was considered positive if normoglycemia was maintained after 6 hours of fast (maximum dose of 15 mg/kg/day)

RESULTS

Initial Presentation Clinical laboratory during hypoglycemia

Total: 8 patients, diagnosed: 7 < 48 hours, 1 at 5 months

2 patients with macrosomia

Maximum glucose infusion rate: 8 -21 mg/kg/min

Glucose: 6-40 mg/dl Insulin: 5-60.6 uUI/l

Δ Glucose post glucagon(>30 confirm HI):37-62 (performed in 3 patients)

β -hydroxybutyrate:0.07-0.3mmol/l (NV:0.03-0.35)

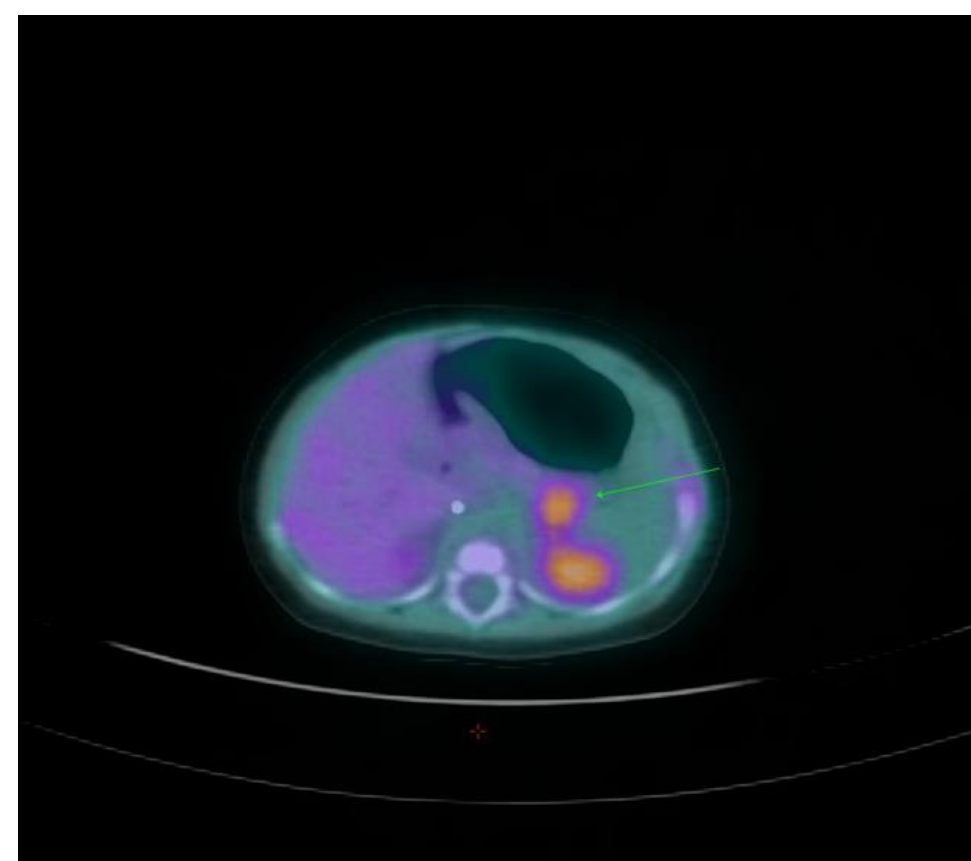
NEFA:0.13-0.5mmol/l (NVO.1-0.9).

All had normal ammonia

18F DOPA-PET-CT scanning

6 patients

4 diffuse 2 focal



Patient with focal disease SUV max 3.3 in tail, the rest SUV max 1.8

Genetic Results:

5 HETEROZYGOUS *ABCC8* mutations were detected in 8 patients evaluated.

3 were identified in 4 diazoxide-responsive patients and 2 in 4 diazoxide-unresponsive patients.

c.2146G>T : Diffuse disease. Diazoxide responsive. Parents DNA were not available

Inherited from unaffected father:

c.2405T>A (diffuse)

c.1792C>T (focal)

De novo

-c.1513G>C Diazoxide responsive. PET scan not performed

-c.4133 G>A Diazoxide responsive, diffuse

RESPONSE TO MEDICAL TREATMENT

Among the 4 who were diazoxide-unresponsive:

- 2 had diffuse disease, one of them had a paternally inherited heterozygous *ABCC8* mutation

- 2 had focal disease: 1 had a heterozygous recessive *ABCC8* mutation the other with normal leukocyte DNA.

In the group who were diazoxide-responsive: 2/4 had diffuse disease the other did not performed PET scan

Side effects: Sirolimus: persistent diarrhea and vomiting, Diazoxide: one patient fluid retention (not under diuretic treatment)

DISCUSSION Among the patients who responded to Diazoxide (4/8) 2 patients had diffuse disease. In the remaining 2 patients 18-F –DOPA–PET-CT could not be performed. In 3 of these patients a heterozygous *ABCC8* mutation was identified. Family member testing was only possible in two of these families and the mutation was shown to have arisen *de novo*.

In the diazoxide-unresponsive group 2/4 had focal disease, one had a heterozygous paternally inherited *ABCC8* mutation and the other has normal leukocyte DNA. In this last patient somatic mutation within the pancreas was not excluded. Among the 2 patients who were diazoxide-unresponsive that had diffuse disease, in one of them no mutation was detected in *ABCC8*, *KCNJ11* or *HNF4A*, in the other the finding of a paternally inherited monoallelic *ABCC8* mutation that predict focal lesion but with diffuse disease suggest that LOH of pancreatic DNA should be rule out to exclude a giant focal lesion. Sirolimus beside the side effects did not improve the glucose levels. Hypoglycemia was not detected in patients with focal disease after the surgical remove of the lesion, whereas incidental hypoglycemia was found in patients under medical treatment.

CONCLUSIONS: The small pancreatic resection guided by 18F-DOPA-PET-CT in focal disease allowed normal blood glucose homeostasis. Patients receiving medical treatment should maintain long-term surveillance to avoid hypoglycemia.