Persistent ketotic hypoglycemia in a carrier of MODY1 : an atypical presentation of heterozygous HNF4A mutations

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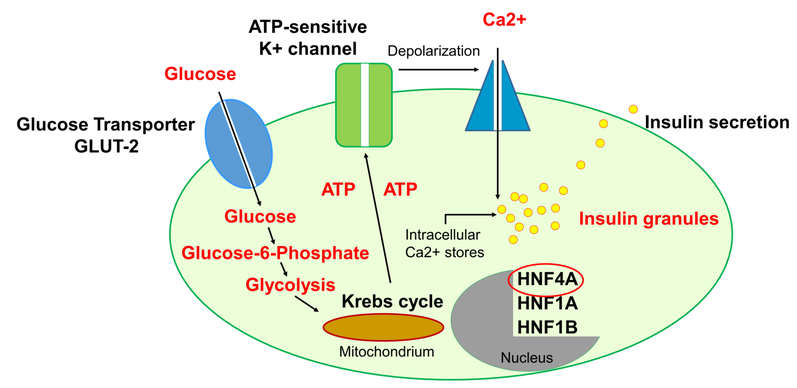
BACKGROUND

Heterozygous loss-of-function HNF4A mutations are known to lead to monogenic diabetes, and in infants, to macrosomia and hyperinsulinemic hypoglycemia. We are presenting a patient with a heterozygous HNF4A mutation presenting with persistent ketotic hypoglycemia and possible dysregulated insulin secretion.

PANCREATIC β CELL FUNCTION



HISTORY

<u>Perinatal Hx</u>:

- Insulin-requring gestational diabetes
- Born at 38 weeks gestation, birth weigh: 4,1 kg
- Hyperinsulinemic hypoglycemia treated with Diazoxide 7,5 mg/kg/day

<u>Past Medical Hx</u>:

- PICU admission at 2 months of age for respiratory distress and hyperglycemia
  ➔ Diazoxide discontinued
- Lengthy hospitalization for persistent hypoglycemia with investigations suggesting exogenous insulin administration:

LABORATORY	RESULT
Blood glucose	1,7 mmol/L
Insulin	772 pmol/L
C-Peptide	25 pmol/L

- Congenital hyperinsulinism genetic panel: Pathogenic variant of HNF4A

<u>Present illness Hx:</u>

- At 7 months, recurrent ketotic hypoglycemia
- Observed as soon as 1h post-prandially
- Persisted while under observation at the hospital and while wearing a continuous glucose monitor at home.

INVESTIGATIONS

Critical samples obtained during hypoglycemia:

LABORATORY	RESULT
Insulin	1,1 – 5,2 pmol/L
βOH-butyrate	1,30 – 2,30 mmol/L
Cortisol	667 nmol/L
Growth hormone	1,27 µmol/L

Other investigations:

Test	Result
Glucagon challenge test	BG increased < 1,7 mmol/L
GSD genetic panel	Negative
Acylcarnitine profile	Normal
Urinary organic acids	Normal
Toxciology screen	Negative
Liver enzymes	Normal
Abdominal ultrasound	Normal aspect of liver

EVOLUTION

Therapeutic trials:

- Corn starch 5-10 g q 4-6h with milk: persitence of hypoglycemia
- Octreotide s/c 15 mcg/kg/day: diarrhea and greyish stools 24h after introduction
- Diazoxide 5mg/kg/day + hydrochlorothiazide 1 mg/kg/day: resolution of hypoglycemia

CONCLUSIONS

Heterozygous HNF4A mutations may present as ketotic hypoglycemia, and laboratory investigations may not suggest hyperinsulinism. Dysregulated insulin secretion, down-regulation of GLUT2 as a result of the known HNF4A mutation vs. an additional condition predisposing to hypoglycemia were considered as possible mechanism to explain this presentation.

55ESPE 550--P1

Perinatal Endocrinology

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DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS 10-12 SEPTEMBER

PosterSessionOnline.com