P2-295

Sirolimus therapy in a infant with congenital hyperinsulinism

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Introduction

- Congenital hyperinsulinism (CHI) due to mutations in ATP sensitive potassium channel (K_{ATP}) in the pancreatic beta cells are the most common and the most severe forms of CHI which was usually unresponsive to diazoxide and octreotide.
- Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is recently suggested as efficient and safe medication as refractory CHI of infants.
- We present an infant with refractory CHI, who responded to Sirolimus

Case presentation

Patient

- A neonate who presented severe hypoglycemia on the first day of birth. (Initial serum glucose level <10 mg/dL)
- Gestational age 34^{+4} weeks, birth weight 2.94kg (>90 percentile)

Critical sample

Postnatal age	3 days	4 days
Glucose (mg/dL)	29	44
Insulin (μIU/mL)	23.5	100.7
Total ketone	10	19
β-hydroxybutyric acid	<4.0	<4.0
acetoacetate	-	-
Cortisol (μg/dL)	10.5	5.6
Growth hormone (ng/mL)	25.77	18.41

***KCNJ11* analysis:** C406C>7, pArg136Cyst, heterozygote

Initial management

- Intravenous glucose infusion rate: 18-22 mg/kg/min
- Glugacon continuous infusion: maximum 5 μg/kg/hr
- High carbohydrate feeding in every 2 hours
- Diazoxide trial for 4 days: maximum 20 μg/kg/day ➔ Ineffective
- Octreotide (Sandostatin®) subcutaneous injection: 40 μg/kg/day, #4

Laparoscopic near total pancreatectomy at the age of 3 months.

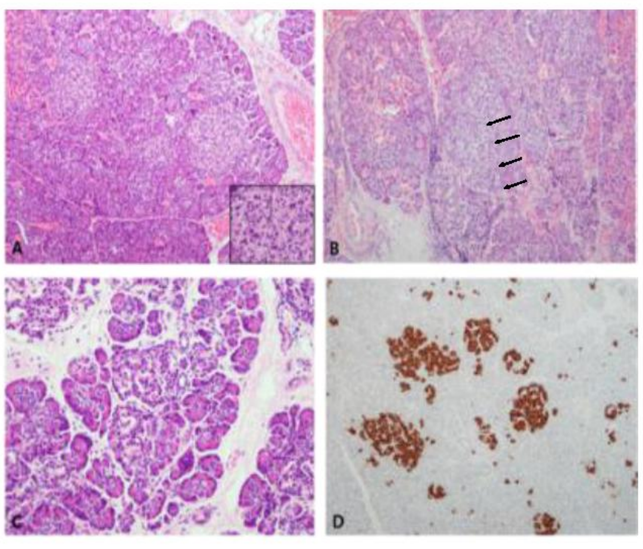

Figure 1. Representative microscopic findings. (A) Enlarged islets were diffusely present throughout the lobules and some enlarged islet cell nuclei were seen (higher magnification in inset). (B) Focal islet cell aggregation with thin rims of acinar cells (arrow) and preserved pancreatic lobular architecture in an area of focal nesidioblastosis. (C) Ductuloinsular complexes were present in both the focal and diffuse nesidioblastosis (A-B. Hematoxylin and eosin, x100, C. hematoxylin and eosin, x200). (D) Immunohistochemistry for insulin highlights the increased beta-cells (Insulin, x100).

Clinical course after near total pancreatectomy

- He presented hypoglycemia 7 hours after operation.
- IV glucose infusion increased and the dose of octreotide was increased to 35 μg/kg/day.

Sirolimus

- At the age of 4 months (1 month after near total pancreatectomy), he started taking Sirolimus 0.2 mg per day.
- The dosage of Sirolimus was increased with monitoring serum Sirolimus levels.
  - Target blood glucose: >60 mg/dL
  - Target serum Sirolimus level: 5-15 ng/mL

Clinical data after initiating Sirolimus

Age (days)	119	120	123	128	131	179	193	234	263
Days *	0	1	4	9	12	60	74	115	144
Dose of Sirolimus (mg)	0.2	0.4	0.5	0.6	0.6	1	1.5	2	2.5
Octreotide (μg/kg/day)	35	35	25	21	12	4	2	0.5	0
IV glucose (mg/kg/min)	4.5	4	3.8	1.3	0	0	0	0	0

*** Days after starting Sirolimus**

Fasting test at 10 months old:

- Serum glucose: 82 mg/dL, plasma insulin: 8.5 μIU/mL

Clinical outcome estimated by 12 months old

- Developmental milestone was normal.
- No other side effect of sirolimus such as serious infection, hyperlipidemia, decrease renal function for 8 months.
- Mild aspartate aminotransferase (AST) elevation

Conclusion

- Sirolimus was effective in maintaining blood glucose level stable in CHI patient with *KCNJ11* mutation in genetic test and with both focal adenomatous hyperplasia and diffuse form pathology.
- There were no major side effect of sirolimus except mild elevation of AST for 8 months of follow up.

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