GENETIC CAUSES OF CONGENITAL HYPERINSULINISM IN SLOVAKIA

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INTRODUCTION AND AIM

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants with incidence of 1:5000 live births (Bruining, 1990) due to insulin hypersecretion.

Genetically, CHI is a heterogeneous condition with mutation in several key genes involved in the insulin secretion. The most common mutations are in KCNJ11 and ABCC8 genes (coding potassium channel subunits), much rarer are mutations in GCK, HNF4A, HNF1A, HNF1B, GLUD1, UCP and SLC16A1 genes. However, the etiology of more than 50% of CHI patients is unknown. The type of β-cell hyperplasia/diabetes forms can be inherited in both recessive or dominant manner; focal forms are sporadic and can arise either from maternal allele deletion or paternall segamental isodisomy (Fig. 1).

Treatment of choice for CHI is diazoxide, however ABCC8 and KCNJ11 recessive and focal forms are diazoxide resistant and other medication or surgery. This study aimed to evaluate genetic cause of severe hypoglycemia and recommend an appropriate therapeutic approach in particular cases.

METHODS

For genetic testing 1,6 unrelated probands with CHI were referred throughout Slovakia over years 2004 – 2014. Inclusion criteria: insulin levels >2µU/ml by plasma glucose < 3,0mmol/L. DNA analysis: direct sequencing of ABCC8, KCNJ11, HNF4A, GCK and HNF1A genes. One patient [HI-48] had whole exome sequencing (BGI, Hong Kong).

RESULTS

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<tr>
<th>Incidence of CHI in Slovakia</th>
<th>1:34 375 live births</th>
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<td>Mutation was identified</td>
<td>in 6/16 (37.5%) patients</td>
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<td>Genotype &amp; diazoxide sensitivity determined the therapy choice</td>
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Diazoxide resistant forms: 3/16 patients (19%)

Case 1 (ID 9586):
- At presentation: 
  - Hypoglycemia: 0.9mmol/L 
  - Insulin in hypoglycemia: 1.95mmol/L 
  - Surgery: partial pancreatectomy
- Diazoxide DNA diagnosis: 
  - Paternally inherited ABCC8 mutation intron 22 (c.2649+1G>C) (novel) – focal form

Case 2 (ID 9572):
- At presentation: 
  - Hypoglycemia: 0.1mmol/L 
  - Insulin in hypoglycemia: 90.8µU/ml 
  - Surgery: partial pancreatectomy
- Diazoxide DNA diagnosis: 
  - Paternally inherited ABCC8 mutation intron 22 (c.2649+1G>C) – focal form

Case 3 (ID 9636):
- At presentation: 
  - Hypoglycemia: 0.8mmol/L 
  - Insulin in hypoglycemia: 90.8µU/ml 
  - Surgery: partial pancreatectomy

Diazoxide sensitive forms: 13/16 patients (81%)

Case 4 (ID 948):
- At presentation: 
  - Hypoglycemia: 0.8mmol/L 
  - Insulin in hypoglycemia: 2.8mmol/L
- Surgery: partial pancreatectomy

CONCLUSIONS

Incidence of CHI in Slovakia is 1:35 000 live births. We have resolved etiology in 37.5% (6/16) CHI cases, with ABCC8 mutations as the most common. The knowledge of the genetic etiology of CHI helped us to choose the most appropriate therapeutic approach.

REFERENCES


Authors certify that there is no conflict of interest with any financial organization regarding the material discussed.