Genotype-phenotype associations in 90 children with congenital hyperinsulinism

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Background

Congenital hyperinsulinism (CHI) is a common cause of hypoglycaemia in neonates, infants and children. CHI is a heterogeneous disease in terms of clinical presentation, genetics and histology.

Objectives

To describe the clinical characteristics, genotype-phenotype correlations and treatment outcome of Russian patients with CHI .

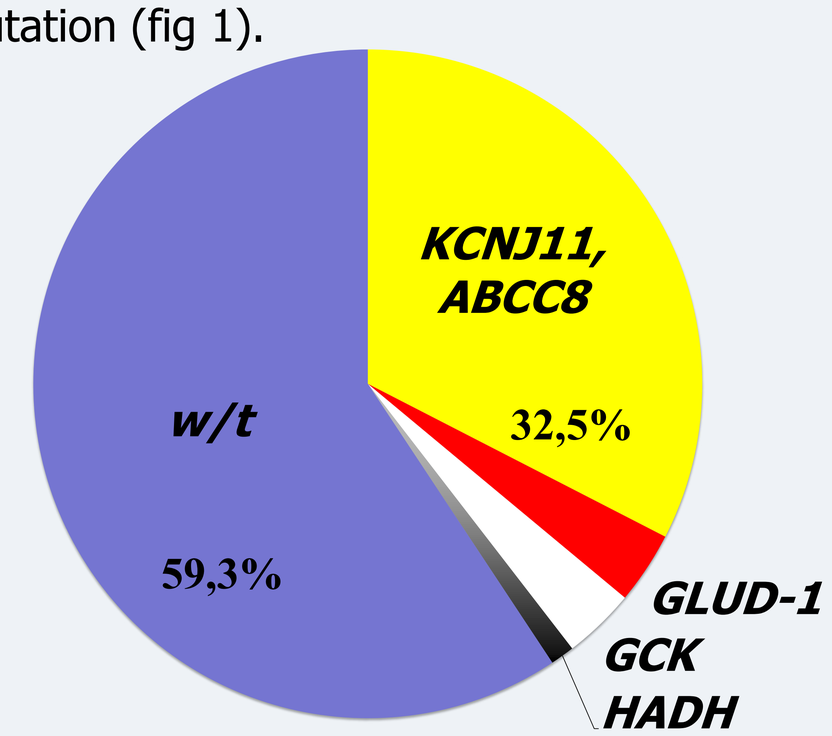
Materials and Methods

A total of 90 children with CHI were identified from 2009 till 2015 in Russia, of which 64 (71,1%) responded to the medical therapy (diazoxide and/or octreotide) and 26 (28,9%) were resistant and underwent subtotal or partial pancreatectomy.

Results

Mutations in *ABCC8* and *KCNJ11* genes were found in 28/86 patients (32,5%); 3/86 patients (3,4%) were found to carry heterozygous *GCK* mutations; 3/86 (3,4%) - *GLUD1* mutations and 1 patient (1,1%) had *HADH* mutation (fig 1).

Fig 1



- Among medically resistant cases, 17/26 patients (65,4%) had K_{ATP} genes mutations, of which 9 were paternally inherited and represent focal HI, what was confirmed histologically and 8 had diffuse disease (4 heterozygous de-novo mutations and 4 homozygous and compound heterozygous mutations); 1 patient (3,8%) had severe *GCK* mutation; 8/26 patients had wild type genes.
- Among medically responsive cases, 11/64 patients (17 %) had mutations in K_{ATP} genes, interestingly 2 of them (both with heterozygous intronic mutations) spontaneously resolved during 6 months after diagnosis; 2/64 (3,1%) – in *GCK*, 3/64 (4,6%) – in *GLUD1* and 1/64 (1,5%) – in *HADH* gene.

We compared main clinical and biochemical features of children with found mutations in *ABCC8* and *KCNJ11* genes (group A) and patients with wild type genes (group B) (Tab 1)

Table 1. Genotype-phenotype associations

	Group A (n=28)	**Group B (n=51)**	**p**
Age at hypoglycaemia manifestation (months) Mean [25%-75%]	0.03 [0.03-0.06]	3.25 [0.06-6]	**0.0009**
Insulin level during the hypoglycaemia (U/l) Mean [25%-75%]	18.3 [7.6-34.8]	10.82 [6.8-27.7]	0.44
Birth weight (g) mean (±SD)	4010 ± 511.8	3314 ± 440.8	**0.04**
Number of medically resistant cases (n, %)	17 (61%)	9 (17%)	**0.002**
Follow up studies (6 months-6 years)	**n=28**	**n=44**	
Cases of spontaneous resolution (n)	2	4	0.7
Severe developmental delay (n; %)	21; 75%	8; 18%	**<0,05**
Cerebral palsy n (%)	15 (53,5%)	4 (9%)	**< 0,05**
Optic neuropathy n (%)	5 (17,85%)	-	**<0,05**
Epilepsy n (%)	11 (39,2%)	5 (11,4%)	**< 0,05**

Conclusions

In conclusion, a genetic cause was detected in 26%, and 69%, of children with mild, and severe CHI, respectively, in Russia. Mutations in ABCC8 and KCNJ11 were found to be the most common cause and associated with severe course of the disease and poor neurologic outcome.

The authors having nothing to disclose

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