CLINICAL AND MOLECULAR CHARACTERISTICS OF TURKISH PATIENTS WITH CONGENITAL HYPERINSULINISM: A SINGLE-CENTER EXPERIENCE

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Introduction and Objectives

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia that needs a prompt diagnosis and relevant treatment to avoid brain damage.

Heterogeneity of CHI is based on not only to clinical presentation and response to treatment but also to histological layout and underlying molecular basis. Mutations in 11 key genes (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *UCP2*, *HNF4A*, *HNF1A*, *HK1* and *PGM1*), that are involved in the regulation of insulin secretion from pancreatic β-cells, have shown to be associated with monogenic forms of hyperinsulinism.

In this study, we describe the clinical and molecular characteristics of a group of Turkish patients with CHI in a single center.

Patients and Methods

Fifty-seven patients (51 families) presenting with CHI to pediatric endocrinology clinic at Kanuni Sultan Suleyman Training and Research Hospital (Istanbul, Turkey) between January 2001 to July 2016 were recruited. Detailed clinical and biochemical data at the time of diagnosis and during follow-up were collected from the past records of the patients. Genetic analysis was performed in Exeter, UK.

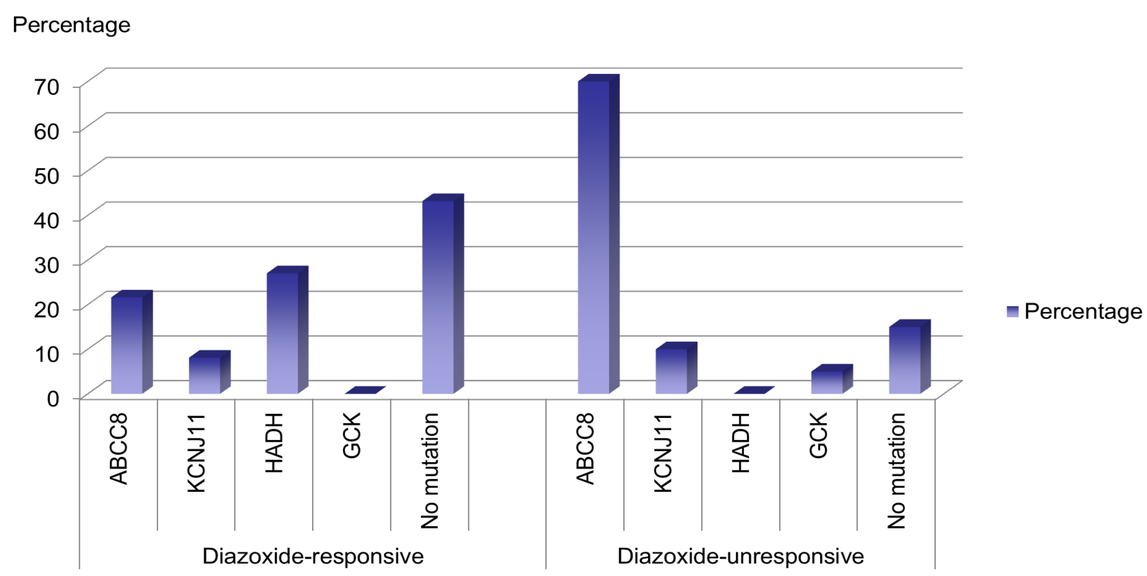
Results

Clinical features of our patients with CHI are summarized in table 1. As ^{18}F-DOPA-PET CT had never been available in Turkey, differentiation between diffuse and focal disease could not be done. Therefore, a near-total pancreatectomy was the only option for all patients requiring surgery.

Table 1. Clinical and biochemical characteristics of patients with CHI

	Results
Clinical characteristics	
Number of patients, *n*	57
Sex (M/F)	38/19
Gestational age, weeks (range)	39 (31-40)
Birth weight, g	3499 ± 911
LGA, *n* (%)	27 (47.4%)
Age at presentation (range)	1w (1w – 13 years)
Consanguinity, *n* (%)	26 (45.6%)
Biochemical characteristics	
Blood glucose, mg/dL	34 (18-45)
Serum insulin, mU/L	29 (1.5-166)
Treatment outcome	
Diazoxide responsive, *n* (%)	37 (64.9%)
Pancreatectomy, *n* (%)	15 (26.3%)

Figure 1. Results of mutation analysis in diazoxide responsive vs. unresponsive patients with CHI



Mutations were found in 38 (66.7%) patients; *ABCC8* (22), *KCNJ11* (5), *HADH* (10), *GCK* (1).

Detection rate of a pathogenic mutation in diazoxide-unresponsive patients (17/20; 85%) was higher than the diazoxide-responsive group (21/37; 56.8%) (p=0.04). Frequency of gene mutations due to diazoxide responsiveness are shown in Figure 1.

While 71.1% of the mutations were homozygous/compound heterozygous, 26.3% heterozygous and 2.6% were *de novo*.

Discussion

Previous studies reported 45.3-78.8% mutation rate in CHI patients. While *ABCC8/KCNJ11* mutations were the most common identifiable cause, *GLUD1* mutations were found to be the second most common mutation in large studies of western countries. In our study, we did not find any *GLUD1* mutation and *HADH* mutations constituted the second most common cause.

Consistent with the previous studies, the majority of diazoxide-unresponsive patients had a K_{ATP} channel mutation.

A mutation in *ABCC8* gene (p.L1171fs, c.3512delT) which was detected in six patients from three families, had also been previously reported in five patients by Demirbilek et al, possibly suggesting a founder effect.

Conclusion

In this large Turkish cohort with CHI, *HADH* mutations were determined as the second most common genetic cause.

For prediction of phenotype of patients with CHI, further investigations in molecular genetics are needed.

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