Clinical characteristics and molecular analysis of Turkish patients with congenital hyperinsulinism

A Single-Centres Experience with 15 cases

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Objective: Congenital hyperinsulinism (CHI) is the most common cause of hypoglycaemia in children. Early identification and management is crucial to prevent irreversible brain damage. CHI has a heterogeneous clinical presentation, histology and molecular biology. We aim to discuss the clinical characteristics and genotype-phenotype correlations of Turkish CHI patients from a single centre.

Design and methods: A total of 15 patients with CHI were recruited from one paediatric endocrine centre in Turkey. Patients with secondary hyperinsulinaemic hypoglycaemia (HH) due to IUGR, perinatal, asphyxia or maternal diabetes mellitus were excluded. All patients had normal acylcarnitine and urine organic acid profile. *ABCC8* and *KCNJ11* were sequenced in all patients and if no mutations were identified *HADH* sequencing was performed.

Results: A genetic diagnosis was made in 9 (60%) patients (*HADH* n= 5, *ABCC8* n=2, *KCNJ11* n= 2). Diazoxide unresponsiveness was observed in one patient with a *KCNJ11* mutation who was managed with subtotal pancreatectomy. Among the diazoxide-responsive patients (n =14), mutations were identified in 8 cases (57%). Genotype-phenotype studies showed that *ABCC8* and *KCNJ11* mutations resulted in increased birth weight and *HADH* mutations were associated with liver dysfunction progressing from mild to severe disease.

Patient No	Gender	Age at Diagnosis	Current Age (Years)	Birth Weight (gr)	Insulin mIU/mL	Glucose mmol/L	Responseive to diazoxide	Duration of Diazoxide Treatment	Mutation	Additional Information
1	M	7 days					Yes	Ongoing	HADH gene p.R236X c.706C>T Homozygous	Liver Dysfunction Hyperammonemia Wilson's Disease (genetically confirmed)
2	F	2 months	3.5	2700	12	1.7	Yes	Ongoing	HADH gene p.L222fs c.664_668del Homozygous	Liver Dysfunction Hyperammonemia
3	F	7 days	4.6	3400	43.2	1.7	Yes	Ongoing	HADH gene p.L222fs c.664_668del Homozygous	Liver Dysfunction Hyperammonemia
4	F	4 months	5.5	3650	36	1.1	Yes	Ongoing	HADH gene R236X c.706C>T Homozygous	Mild Liver Dysfunction Hyperammonemia
5	M	4 months	0.5	3300	28	1.7	Yes	Ongoing	HADH gene p.R236X c.706C>T Homozygous	Mild Liver Dysfunction
6	F	7 days	0.5	4500	30	1	Yes	Ongoing	ABCC8 Q1488R c.4463A>G Heterozygous	
7	M	7 days	4.9	4500	1	2	Yes	1 year	ABCC8 p.N1481S c.4442A>G Heterozygous	
8	F	7 days	4.5	4000	15.2	1.5	No	Pancreatectomy	KCNJ11 p.E126K c.376G>A Homozygous	Mental Retardation
9	F	4 months	5.1	3350	5.7	2.2	Yes	Ongoing	KCNJ11 p.A362T c.1084G>A Heterozygous Variant of uncertain significance	
10	F	7 years	23	3200	8,33	2,5	Yes	15 years	Ø	Epilepsy
11	F	7 days	4.8	2350	10	2.4	Yes	7 months	Ø	
12	M	6 months	5.8	4150	6.6	1.4	Yes	Ongoing	Ø	
13	F	7 days	7	4570	6	1.6	Yes	5 months	Ø	
14	M	5 months	16	3100	2.3	1.2	Yes	6 years	Ø	Special Education
15	F	3 days	2.5	3500	4	1.1	Yes	Ongoing	Ø	

Conclusions: Our results are different from previous studies from Turkey which report recessive *ABCC8* and *KCNJ11* mutations as the most common cause of CHI. We identified mutations in 3 different genes in 57% of diazoxide-responsive patients which is a higher pick-up rate compared to other studies. Homozygous *HADH* mutations are a rare cause of CHI but in our cohort they accounted for 33% of cases. Hepatic dysfunction, cardiomyopathy or effects on skeletal muscle have not been reported in patients with *HADH* mutations to date. This work therefore extends the phenotype associated with these mutations.

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