TITLE

Clinical characterstics, genotype and phenotype correlations and follow up of patients with hyperinsulinaemic hypoglycaemia; A single center experience from a southeastern city of Turkey

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OBJECTIVES

CHI is a clinically, genetically and histologically heterogenous diesease. In recent years substantial developement have been observed in the genetics, imaging techniques and tretment options. We, herein, reports the clinical characteristics, genetics and follow-up of 31 CHI patients from a single paediatric endocrine center with a particular emphasis on the new treatment options.

METHODS

Clinical characteristics, biochemical features and molecular genetics analysis, treatment options and longterm follow up of patients with CHI was collected from the patients' hospital files.

RESULTS

The number of patients recruited was 31(18 females). A mutation was detected in 16 out of 23 (%69.5) patients who a molecular genetics analysis performed. Of which 15 had mutation in *ABCC8* and one in *HADH*. All patients with an *ABCC8* mutation were diazoxide unresponsive. Five were underwent surgery. Two patients were managed with sirolimus until their ages of 3 and 10 months when sirolimus stopped due to hepatotoxicity. Post-sirolimus trial of octreotide treatment achieved normoglycaemia and patients did not require pancreatectomy. In total 10 patients was managed with the long-acting somatostatin analogs, octreotide LAR/lanreotide. A female with homozygous *ABCC8* mutation developed diabetes at the 4th year of octreotideLAR treatment, when she was 15 years-old (HbA1c:8%). Hyperglycaemia is now being succesfully managed with dietary intervention. All of the other 9 patients with *ABCC8* mutation, including her younger brother with identical mutation, are being managed with octreotideLAR succesfully and with no severe side effects. One patient with *HADH* mutation has protein sensitive, diazoxide responsive CHI. She is now 8 years-old and has a good neurodevelopemental outcome. 6 out of 8 patients who a mutation analysis was not available were diazoxide responsive. Treatment of 2 patients was switched to the LAR due to poor compliance to the diazoxide therapy.

Table 1. Phenotype genotype characteristics and follow up of 16 patients with a mutation result

Pt/sex	Current age (years)	Age at diagnosis (day)	Gene	Mutation	Zygosity	Treatment			Current treatment	Follow up
						Diazoxide	Octreotide	Pancreatectomy		
1/M	5	2	ABCC8	p.Ala1185Glu	Homozygous	-	+		LAR	Delay in speech, Feeding with N/G tube
2/F	8	30	ABCC8	p.Ala1185Glu	Homozygous	-	+/-		LAR	Developemental delay Epilepsy
3/F	9	NA	ABCC8	p.Ala1185Glu	Homozygous	NA	NA		-	Sister of patient 1 Admitted at the age of 9 years Severe neuro-developemental delay Epilepsy
4/M			ABCC8	p.Leu533Pro (p.L533P)	Homozygous	-	+/-			Died due to sepsis at another clinic at the age of 2 months
5/M	4.5	5	ABCC8	p.Ala1185Glu	Homozygous	-	+		LAR	Mild neurodevelopemental delay Poor compliance
6/F	3	6 months	ABCC8	N1349fs Heterozigot	Heterozygous (Paternal)	-	+		LAR	Normoglycaemic Normal neurodevelopement
7/F	3	1	ABCC8	A1185E	Homozygous	-	-/+		LAR	Received sirolimus for 3 months. Subsequently good response to the octreotide MDI than replaced to the LAR Now is normoglycemic with monthly LAR Normal neurodevelopement
8/F	3.5	1	ABCC8	H59P	Homozygous	-	-		LAR	Received sirolimus for 10 months. Subsequently good response to the octreotide MDI than replaced to the LAR Now is normoglycemic with monthly LAR Normal neurodevelopement
9/F	13,9	7	ABCC8	p.Leu1171fs (p.L1171fs)	Homozygous	-	+		Off-medication	Severe neurodevelopmental delay Developed diabetes mellitus at the 3rd year of LAR treatment
10/M	9,9	7	ABCC8	p.Leu1171fs (p.L1171fs)	Homozygous	-	+		LAR	Normoglycemic with monthly LAR Severe neurodevelopemental delay
11/M	NA	15	ABCC8	p.Leu1171fs (p.L1171fs)	Homozygous	-	-	+ (42 days)	Missed f/up visits	Cured Did not come regular follow up visit post-surgery Histology: Diffuse
12/M	-	10	ABCC8	p.Arg168Cys (p.R168C)/p.Asn188Ser (p.N188S)	Compound heterozygous	-	-	+ (40 days)	Exitus	Was normoglycemic at the postsurgical follow up visit of 2 months Had a normal neurodevelopement Died due to hepatic failure of unknown etiology Histology: Diffuse
13/M			ABCC8	p.Leu1171fs (p.L1171fs)	Paternal	-	-			Surgery did not resolve hypoglycemia episodes Died due to postsurgery sepsis Histology: Diffuse
14/F	5	1	ABCC8	p.Leu1171fs (p.L1171fs)		-	-	+(20 days)	Missed f/up visits	Postsurgery was normoglycemic with diazoxide and octreotide Missed follow up visits after 5th month of surgery Histology: Diffuse
15/M	2.5	2	ABCC8	L1171fs	Heterozygous (paternal) and loss of maternal heterozygosity	-	-	+(17 days)	Off medication	Cured Normal neurodevelopement Loss of maternal heterozygosity was shown in resected pancreatic specimen Histology: Focal
16/F	8.5	7 months	HADH	p.Arg236X (p.R236X)	Homozygous	+			Diazoxide	Protein sensitivity (+) Normoglycemic with diazoxide and avoiding from protein rich diet Normal neurodevelopement
17/F	2.4	1	No mutation			+			LAR	Transient elevation of transaminases Normal neurodevelopement
18/F	5	15	No mutation			+/-	+		LAR	Epilepsy and neurodevelopemental delay Transition to LAR due to poor compliance at the age of 2 years Better glycaemia after LAR treatment
19/M	4.5	30	No mutation			+			Diazoxide	Normal neurodevelopement
20/M	1	3	No mutation			+			Off medication	Normal neurodevelopement
21/M	4	4	No mutation			+/-			LAR	Refractable epilepsy despite antiepileptic treatment Diazoxide stopped and LAR commenced at the age of 3.5 years. Normoglycaemic with monthly LAR treatment
22/FM		8	No mutation			+/-	+		Octreotide	Normal neurodevelopement
23/FM	2.3	7	No mutation			-	+		Off medication	Neurodevelopental delay

CONCLUSIONS

In this series of 31 CHI patients from a single paediatric endocrine center we detected a mutation in a high proportion of patients who underwent a molecular genetics analysis. New therapeutic tools landreotide and sirolimus have improved the neurodevelopemental outcome of our both diazoxide responsive and unresponsive patients.

Conflict of interest: Nothing to disclose

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Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)

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