CONGENITAL HYPERINSULINISM: CLINICAL and MOLECULAR CHARACTERİSTİCS– Fluorine-18-L-dihydroxyphenylalanine positron emission tomography (F-DOPA PET) SCAN RESULTS -TREATMENT RESPONSES AND SHORT TERM OUTCOMES OF 5 PATİENTS

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INTRODUCTION AND OBJECTIVES

The most common cause of persistent hypoglycemia and related brain damage in infancy is congenital hyperinsulinism (CHI), due to inappropriate secretion of insülin by pancreatic βcells. The most frequent and most serious mutations are activating mutations in ABBC8 or KCNJ11 genes. Genetic analyses, which might predict the type of lesion, performed in the early period and 18-f dopa pet scanning are very valuable for treatment choice and follow-up of the patients. In this study, our aim was to emphasize the importance of genetic studies and 18 f-dopa pet scanning, and the management of 5 CHI patients with or without known genetics who underwent different treatment strategies.

PATIENTS AND METHODS

Five patients who applied to the pediatric endocrinology clinic at Istanbul University Cerrahpaşa medical Faculty between 2015-2018, were presented in this study. Detailed clinical and biochemical data were collected from patients at the time of diagnosis and during follow-up. Genetic analysis was performed in Exeter, England.
18-f-dopa pet scanning,which is a study supported by Istanbul University research, was performed at Department of Nuclear Medicine of Cerrahpasa Medical Faculty.

CLINICAL CHARACTERISTICS

Clinical features of our patients with CHI are summarized in table 1.
Four cases were diagnosed in the first month of life, while one case was diagnosed at fourth months. All of the patients had presented with hypoglycemic seizures. There was a history of preterm delivery in 4 cases. Four patients were large for gestational age and one had a normal birth weight. Female/male ratio was 4:1. There were consanguineous marriages between parents in three cases. While one case responded to diazoxide, three cases needed additional therapy. In one case pancreatectomy was performed due to the failure of medical therapy. Four cases were scanned with 18-f dopa pet CT (Fig 1-3). In 2 cases, lesions were interpreted as focal; increased uptakes were observed in the head and body of the pancreas. While 3 cases showed normal motor mental development, severe motor mental retardation (MMR) was observed in one case due to hypoxic enchephalopatic disease. And one case diagnosed at the 4.mounth showed moderate MMR due to hypoglycemia. Genetic analyzes were performed in all cases. Mutations in ABCC8 genes were detected in 3 cases. In 2 cases no mutation was found in the studied genes. Detailed clinical ,biochemical and radiological data are presented in Table 1.

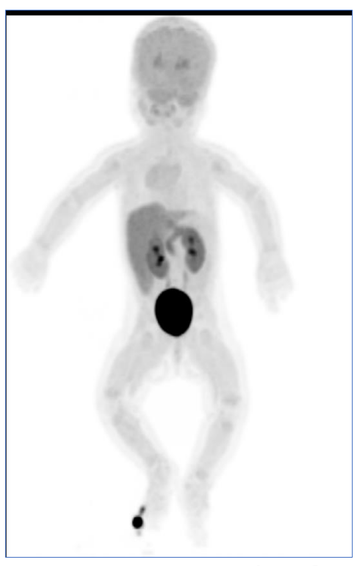

Fig1: Case 1 normal 18-f dopa pet scan

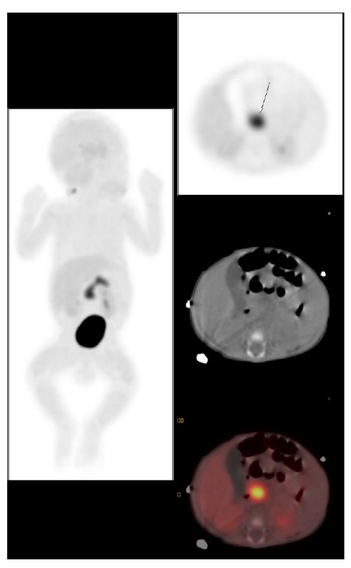

Fig 2: Case 4
Early dynamic images showed increased uptake In the pancreas head like a focal pancreatic lesion

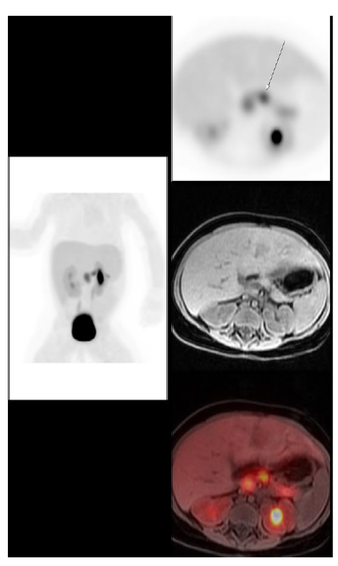

Fig 3: Case 5
It is compatible with focal incresed uptake image of 0.5 cm in the pancreas body.

***Table 1*: Clinical, biochemical , genetic and radiologic data of patients**

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
AGE (year)	1,46	3,67	2,25	1,07	0,45
GENDER	female	Female	Female	male	Female
GESTATIONAL AGE(WKS)	33	29/6	36/6	37/5	36
BIRTH WEIGHT (gr)	2580	2300 gr	3000	2350	2900
WEIGHT FOR GESATTIONAL AGE	LGA	LGA	LGA	AGA	LGA
CONSANGUINEOUS MARRIAGE	3º relatives	None	None	2º AKRALIK +	3º AKRALIK +
AGE OF DIAGNOSIS	1/365 GÜN	20/365 gün	4/12 AY	2/365 GÜN	1/365 GÜN
COMPLAINT AT DİAGNOSİS	SEIZURE	SEIZURE	SEIZURE	SEIZURE	SEIZURE
TODAY					
HEIGHT (sds)	78 cm(-1,07sds)	96 cm (-1,10)	85 cm (-0,1)	75 cm (-1,08)	58 cm (-2,86)
WEIGHT (sds)	9,2 kg (-1,2sds)	25 kg (+ 3,49)	12 kg (0,35)	8,5 kg (-1,52)	6,1 kg (-1,6)
BMI (sds)(kg/m2)	15,1 (-0,8 sds)	27,1 (+4,82)	16,7 (0,44)	14,2 (-2,1)	17,5 (0,4)
LABORATORY FINDINGS					
GLUCOSE (mg/dl)	49	40	25	48	48
INSULIN (µU/ml)	78,9	43,2	4,4	18,8	33,5
C PEPTİDE (ng/ml)	7,08	5,7	2,1	1,95	4,98
CORTISOL (µg/dl)	8,86	14,8	8,5	3,17 (normal response to low dose ACTH stimulation test)	21,2
GROWTH HORMONE (ng/ml)	10,8	8,7	3,85	11,6	10,07
URINARY KETONE	Negative	Negative	Negative	Negative	Negative
GLUCAGON RESPONSE	Not evaluated	Not evaluated	+	+	+
METABOLIC SCANNING	Normal	Normal	Normal	Normal	Normal
GENETIC ANALYSES					
PATIENT	Heterozygous missense mutation on ABCC8 Exon 16'da c.2143G>A p.V715M	Compound Heterozygous mutation on ABCC8 Exon 19 ve 37 de c2371G>T/c.4480C>T	No mutation detected	No mutation detected	Heterozygous aberant splicing on ABCC8 intron 9 c.1467+5G>A
MOTHER OF PATIENT	No mutation detected	Heterozygous missense mutation on ABCC8 Exon 37 c.4480C> p.Arg1494Trp	No mutation detected	No mutation detected	Not studied.
FATHER OF PATIENT	No mutation detected	Heterozygous nonsense mutation on ABCC8 Exon 19 da c.2371G>T p.Glu791Terrp	No mutation detected		Not studied.
RADIOLOGICAL EXAMINATION	USG: normal Abdomen Mrg: normal	Usg: hepatosplenomegaly Abdomen mrg: hepatosplenomegaly	Usg: normal Abdomen mrg: hepatosplenomegaly	Usg: normal	Usg: normal
F DOPA PET SİNT	No lesion detected.	Screening was not performed because of the patient's health problem.	Diffuse uptake	In the pancreas head early dynamic images showed increased uptake like a focal pancreatic lesion	It is compatible with focal incresed uptake image of 0.5 cm in the pancreas body.
DIAZOXIDE RESPONSE	No response	No response	No response	responsive	No response
SECOND LINE THERAPY	Octreotide (15 mcg/kg/g)	Octreotide (15 mcg/kg/g) Nifedipine	Octreotide (15 mcg/kg/g) Nifedipine	--	--
SURGİCAL TREATMENT	--	--	--	--	Near total pancreotectomy
NEUROMOTOR DEVELOPMENT	Age compatible	Severe retardation	Moderate retardation	Age compatible	Age compatible
CRANİAL RADİOLOGİCAL SCREENİNG	Mrg: normal	EEG: Pathological wave activity in the left frontal region MRG: common cystic encephalomalacic changes	MRG: normal EEG: epileptic focus in the occipital region	MRG: normal	MRG: normal
ADDITIONAL DISEASE	--	İU listeria inf. İVH + Hydrocephalus +	Epilepsy	Hepatosplenmegaly portohepatic shunt	--

CONCLUSION

Hyperinsulinemic hypoglycemia in neonates and infants is a condition that should be urgently and effectively treated to prevent neurological complications. Molecular genetic tests and 18 F-dopa pet scans in congenital hyperinsulinism are very valuable to decide on treatment choice and to predict the clinical follow-up.