TITLE

Presenting features, clinical characteristics and follow up of familial isolated glucocorticoid deficiency (FGD) due to mutations in *MC2R* and *MRAP* genes

[1,2]Mehmet Nuri Ozbek, [1]Nezahat Doğan Karasin, [2,3]Huseyin Demirbilek, [1]Meliha Demiral, [2]Rıza Taner Baran, [4]Tulay Guran

[1]Gazi Yasargil Training and Research Hospital, Clinics of Paediatric Endocrinology, Diyarbakir, Turkey

[2]Diyarbakir Children State Hospital, Clinics of Paediatric Endocrinology, Diyarbakir, Turkey

[3]Hacettepe University Faculty of Medicine, Department of Paediatric Endocrinology, Ankara, Turkey

[4]Marmara University School of Medicine, Department of Paediatric Endocrinology, Istanbul, Turkey

OBJECTIVES

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterized with isolated glucocorticoid deficiency. Melanocortin receptor 2 (MC2R) mediates the functions of adrenocorticotropic hormone (ACTH) in the adrenal cortex. MC2R accessory *protein* (*MRAP*) is a transmembrane protein which involves in the trafficking of MC2R to the cell surface. Mutations in *MC2R* and *MRAP* genes cause familial acount for FGD type 1 and 2. In present case series we evaluate the clinical characteristics and follow up of 6 cases with FGD due to mutations in *MC2R* and *MRAP*.

METHODS

Data of 6 cases with FGD (5 with mutations in *MC2R* and one with mutation in *MRAP*) who being followed at our pediatric endocrine center was collected from the hospital files. Diagnosis of FGD was considered in case of elevated ACTH in course inappropriately low cortisol level and exclusion of other etiologies. Hydrocortisone replacement was the standart therapy. The results of molecular genetic analysis of the cases were already reported elsewhere*.

RESULTS

Results: The presenting age and complaints, clinical and hormonal characteristics, mutations and follow up of cases are summarized in Table 1. The main presenting complaints were hyperpigmentation, and hypoglycemic convulsion in all cases. During a follow up period of 26 to 115 months, one of the patients with homozygous 560delT mutation in *MC2R,* one female with G226R mutation in *MC2R*, and one female with IVS3ds+1delG mutation in *MRAP* had NDD, while the other 3 patients had completely normal neurodevelopment.

Table 1. Clinical characteristics and follow up of cases

	Age (month) /sex	Presenting complaints	Mutation	At diagnosis				At latest follow up visit				
				Cortisol (mcg/dL)	ACTH (pg/mL)	Weight (SDS)	Height (SDS)	Age (month)	ACTH (pg/mL)	Weight (SDS)	Height (SDS)	Additional features
Case 1	4 mo/F	Hyperpigmentation Hypoglycemia Convulsion	MC2R 560delT	0.04	>1500	4.9 (-0.51)	61 (-2)	61	132	17.8 (-0.31)	103 (-1.33)	-
Case 2	12 mo/F	Hyperpigmentation Hypoglycemia Convulsion IUGR	MC2R 560delT	0.6	2000	12.7 (2.58)	92.2 (5.98)	46	2000	16 (0.11)	108 (1.53)	NDD Spasticity
Case 3	9 mo/M	Hyperpigmentation Hypoglycemia Convulsion	MC2R A233P	0.3	2000	10.7 (1.45)	76.5 (1.78)	66	6.48	20.8 (0.41)	109.3 (-0.88)	-
Case 4	18 mo/F	Hyperpigmentation Hypoglycemia Hypothyroidism	MC2R G226R	1.0	>1250	18.3 (4.67)	96.6 (4.63)	106	19.3	67 (4.07)	138.2 (1.19)	Primary hypothyroidism Obesity NDD
Case 5	5 day/F	Hyperpigmentation Hypoglycemia Convulsion Respiratory distress	MC2R 560delT	0.26	826	2.3 (-2.61)	48 (-0.93)	26	4.49	9.5 (-2.09)	78.5 (-2.75)	-
Case 6	34 Months	Hyperpigmentation Hypoglycemia Convulsion Hyperbilirubinemia	MRAP IVS3ds+1delG	<1.0	>1250	19.7 (2.99)	102.2 (2.03)	115	38.4	61.3 (3.18)	136.5 (0.15)	NDD Obesity Epilepsy

CONCLUSIONS

In this series evaluating a small number of FGD due to *MC2R* and *MRAP* mutations, we observed that patients with early diagnosis and compliant to the hydrocortisone therapy had a normal neurodevelopment, while, delay in diagnosis and poor compliance was associated with severe hypoglycemic convulsions and associated NDD.

**Guran T, et al, JCEM 2015*

Conflict of interest: Nothing to disclose