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PRECOCIOUS PUBERTY IN PATIENTS WITH PRIMARY ADRENAL INSUFFICIENCY DUE TO *MELANOCORTIN RECEPTOR 2* MUTATION

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Nothing to disclose.

Background

Precocious puberty has a complex and polygenic etiology. To describe genetic factors affecting onset and regulation of puberty and pathophysiology of precocious puberty, further studies are needed. *MC2R* is expressed in the adrenal cortex and has a major role on the control of hypothalamo-pituitary-adrenal axis. It is reported that ACTH receptor *MC4R* has impact on premature adrenarche. Melanocortin signaling system is reported to have leptin mediated effect on the regulation of GnRH neuron activity and has an important role in the onset of puberty and fertility.

Objective

To evaluate the early onset puberty of patients with primary adrenal insufficiency (PAI) due to Melanocortin Receptor 2 (*MC2R*) gene mutation.

Patients and Methods

Four patients (3M,1F) with PAI, two of whom are siblings (P#2&#3) were included in the study. Age of diagnosis of PAI was between 1 day-11 months, all of them presented with hypoglycemic convulsion. Follow up period was 7.6-20.4 years. They were from consanguineous families. All of the patients were born term and appropriate for gestational age.

The patients were evaluated at presentation, onset of puberty and at recent visit.

All patients had severe homozygous *MC2R* mutation (c.560delT, p.V187Afs*29) causing PAI (Guran T et al, 2016). P#1, #2 and #3 had central precocious/early puberty started at 9.5, 8.4 and 7.4 years, respectively. The onset of puberty of the P#4 was at the age of 8.5 years. At onset of puberty, the P#3 had obesity, the P#4 was overweight. LH, T/E2 levels of the patients were in pubertal ranges. Tumor markers were negative and no adrenal rest/tumor were detected in testes/ovaries. Puberty had rapid progression in P#2 and GnRH analogue was started at 11 years of age.

Final height of P#1 was -2.6 SDS. Age of menarche of P#4 was 11 years.

Table 1. Clinical and laboratory features of the patients

	P #1	P #2*	P #3*	P #4
Age of diagnosis (PAI)	1 day	11 months	1 day	12 day
Gender	M	M	M	F
Birth weight SDS	-0.1	0.3	1.2	0.7
Mother's age at menarche (yrs)	13	11.5	11.5	12
Target height SDS	-1.0	-1.0	-1.0	-1.4
At presentation				
Age (months)	0.5	11	1	6.5
Weight (kg)/SDS	3.2 / -1.8	11.4 / 1.1	3.8 / -0.9	
Heght (cm) /SDS	50 / -1.5	80.7 / 1.7	49.9 / -1.5	
ACTH (pg/ml) (N:7.2-63.3)	958	>1250	>1250	194.1
Cortisol (µg/dl)	0.1	0	1.2	<0.01
PRA (ng/ml/h) (N: 1.9-6.0)		7.7	1.9	3.2
Glucose (mg/dl)	17	15	39	40
Additional problems	Mental-motor retardation and autism	No	No	Congenital hypothyroidism
At onset of puberty				
Age (years)	9.5	8.4	7.4	8.5
Weight (kg) /SDS	28.5 / -0.4	30.1 / 0.6	34.8 / 2.1	40.2 / 1.9
Height (cm) /SDS	125.6 / -1.5	128.3 / -0.2	126.0 / 0.4	142.0 / 2.3
BMI SDS	-0.5	0.9	2.3	1.38
Pubertal stage	2	2	2	2
Testes volume (ml) (Prader)	4 /4	4/4	4/4	
Bone age (yrs)	7	8	6	7.8
ACTH (pg/ml)	1250	5.15	147.4	1250
Basal LH (mIU/ml)	0.6	1.3	0.7	2.2
Basal FSH (mIU/ml)	1.0	1.7	0.81	1.7
GnRH test peak LH /FSH (mIU/ml)	6.8 / 2	13.1 / 4.5	4.13	3.93
T (ng/ml) / E2 (pg/ml)	0.28 / -	3.29 / -	0.3 / -	- /9.9
Scrotum / pelvic US Testis volume (ml) (R/L) Uterus/Ovaries	R: 2.9 L: 3.9	R: 2.3 L: 1.8	R: 1.4 L: 1.2	Uterus: 3.6 ml R Ovary: 0.8 ml L Ovary: 1 ml
Treatment	HC	HC + GnRHa	HC	HC + L-T4
At recent evaluation				
Age (years)	20.8	12	7.8	14.1
Weight (kg) /SDS	53.8 / -2.2	49 / 0.5	37.6 / 2.2	78.4 / 2.9
Height (cm) /SDS	160.5 / -2.6	154.5 /0.6	128.5 / 0.6	164.4 / 0.7
BMI SDS	-0.9	0.3	2.4	2.3
Pubertal stage (Tanner)	5	5	2	5
Testis volume (ml) (Prader)	25 / 25	15/25	4-5 / 4-5	
Bone age (yrs)	18	-	-	16

* Siblings, SDS : Stardart Deviation Score, BMI: Body Mass Index, R: Right , L: Left, US: Ultrasonography

Conclusion

- We report that ACTH receptor-*MC2R* gene mutation and onset and regulation of puberty may be related.
- We also recommend that these patients must be closely followed for pubertal development.

References

1. Neyzi O, Bundak R, Gökçay G, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015; 7(4):280-293
2. Kurtoğlu S, Hatipoğlu N, Mazıcıoğlu MM, Akın MA, Çoban D, Gökoğlu S, Baştuğ O. Body weight, length and head circumference at birth in a cohort of Turkish newborns. J Clin Res Pediatr Endocrinol. 2012;4(3):132-139
3. Guran T, Buonocore F, Saka N, et al. Rare causes of primary adrenal insufficiency: Genetic and clinical characterization of a large nationwide cohort. J Clin Endocrinol Metab 2016; 101(1):284-292
4. Martin MBR, White C, Kammerer C, Feldman Withchel S. Mutational analysis of the melanocortin-4 receptor (MC4R) gene in children with prematüre pubarche and adolescent girl with hyperandrogenism. Fertil Ster, 2004; 82(5): 1460-1461
5. Lampert KP, Schmidt C, Ficher P, et al. Determination of onset of sexual maturation and mating behavior by melanocortin receptor 4 polymorphisms. Curr Biol, 2010; 20: 1729-1734
6. Israel DD, Sheffer-Babila S, de Luca C, et al. Effects of leptin and melanocortin signaling interactions on pubertal development and reproduction. Endocrinology 2012; 153: 2408-2419

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