Insight of differential diagnosis of DAX-1 deficiency from two patients with elevated testosterone in early infancy

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Introduction

DAX-1 is Dosage-sensitive sex reversal - Adrenal hypoplasia congenita critical region on the X chromosome 1, caused by mutation of NR0B1.

It commonly presents X-Linked adrenal hypoplasia congenital, hypogonadotropic hypogonadism and infertility.

However, we observe two patients whose testosterone elevated in their early infancy. which tended to be misdiagnosed as congenital adrenal hyperplasia.

Methods

We observe two cases of DAX-1 deficiency with elevated testosterone during their early infancy and summarize DAX-1's distinct features between congenital adrenal hyperplasia.

Case 1

For case 2, jaundice is his only symptom. His maximal ACTH is up to 2000pg/ml, minimal cortisol is 0.71nmol/L, maximal testosterone is 181ng/ml, serum sodium is 121mmol/L, serum potassium is 9.1mmol/L, and 17-hydroxyprogesterone is 3.01nmol/L (Table 1). Adrenal ultrasound shows hypoechoic nodule in adrenal region which is similar to adrenal gland structure, the size is smaller than normal. Gene test finds NR0B1 （NM_000475.4） Intron1: c.1169-1G>T.

Table 1Hormones outcome and medication dosages

Age	Weight (kg)	ACTH (pg/ml)	Cortisol (nmol/L)	Aldosterone (pg/ml)	Renin (pg/ml)	Luteinizing hormone (mIU/ml)	Follicle-stimulating hormone (mIU/ml)	Testosterone (nmol/L)	Androstendione (ng/ml)	Hydrocortisone	Fludrocortisone	Episodes
1d	3											
14d	2.78							1.24				
22d		172	5.94	243				3.85		3mg/d	0.05mg bid	
47d		11.7						5.72				
57d		119						6.28				
68d	4.6	320.3	179.68			1.32	6.96	5.93		12.5-20mg/d		lower respiratory
77d	5	3.29	>1750	38.76		1.69	6.57	5.41		15mg/d		infection
3M			1613					2.72		8mg/d		
4.5M		3.71	1220					0.98				
6M	7.7	4.99	576					<0.09		5mg/d	0.05mg bid	
9M		34.78	497.6					<0.09		5mg/d		
1Y2M	11.2	176.5	627.6					<0.09		5mg/d	0.05mg bid	
1Y7M		764	453					<0.09				
2Y1M		845.8	146.5					<0.09				
3Y		169.7	531.1					<0.09				
3Y3M	20	443.7	159.9					<0.087		6.25-10mg/d	0.05-0.025mg bid	
4Y		127.3	480.2	62.01	88.3			<0.088		10mg/d	0.033mg bid	
4Y5M	23	196.1	1.12	31.29	32.05			<0.09		12.5mg/d	0.033mg bid	
5Y1M	29.2	>2000	0.71	68.44	120.98	<0.1	0.9	<0.087	<0.3	12.5mg/d	0.075mg qd	

reference value: ACTH: 7.2-63.3 pg/ml, cortisol:171-536 nmol/L, aldosterone:40-310pg/ml, renin:4-38 pg/ml, luteinizing hormone:0.2-1.4mIU/ml, ollicle-stimulating hormone:0.2-3.8mIU/m

Case 2

For case 1, he is a male with uneventful gestation and birth, and has a primary symptom as jaundice. Poor feeding and pigment genital area is observed. His maximal ACTH is more than 2000pg/ml, minimal cortisol is 40.05nmol/L, maximal testosterone is 14.33ng/ml, serum sodium is 118.7mmol/L, serum potassium is 8.1mmol/L, and 17-hydroxyprogesterone is normal. Both sides of adrenal gland are undetectable by adrenal ultrasound. Gene analysis shows pathogenic mutation on NR0B1 （NM_000475.4） Exon1: c.433_434insGGAT.

Results

After the replacement of hydrocortisone and fludrocortisone, their levels of testosterone come down to normal range in 4 months, 6 months respectively.

Bone age of Case 1 is 2.5 years when his chronological age is 3 years and 4 months.

Both of them get smaller testes which is consistent with his disease.

Conclusions

Although DAX-1 commonly occurs hypogonadotropic hypogonadism at puberty or in early adult， gonad and sex hormones could be normal or even temporal elevated in early time.

With this report we can summarize DAX-1's distinct features as follows： 1. DAX-1 is absent from elevated 17-Hydroxyprogesterone in general； 2. DAX-1 occurs delayed bone age which is opposite to congenital adrenal hyperplasia； 3. Adrenal ultrasound has certain value for recognizing DAX-1 and congenital adrenal hyperplasia； 4.Genetic test is an optimal way to distinguish DAX-1 deficiency from other diseases.

References

1. Muscatelli F,Strom TM, Walker AP, et al. Mutations in the DAX-1 gene give rise to both X-linked adrenal hypoplasia congenita and hypogonadotropic hypogonadism. Nature. 1994;372(6507):672-6.
2. Zohar Landau , Aaron Hanukoglu , Joseph Sack , et al. Clinical and genetic heterogeneity of congenital adrenal hypoplasia due to NR0B1 genemutations. Clin Endocrinol.2010; 72(4):448-54.

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Multisystem endocrine disorders
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Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018