CORTISOL RESPONSE TO ACTH STIMULATION TEST IN NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA (NCCAH)

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INTRODUCTION AND OBJECTIVES

- While CAH is associated with deficient cortisol production, NCCAH is characterized by sufficient cortisol response at the cost of androgen overproduction.
- The mechanism(s) responsible for the normal secretion of cortisol in NCCAH remain unclear.
  - ➢Preservation of cortisol secretion in NCCAH is partly explained by the typically limited loss of 21-hydroxylase activity.
  - ➢A generalized adrenocortical hyperresponsivity to ACTH stimulation leading to an exaggerated production of 11-deoxycortisol has also been suggested
- In contrast to the above reports, there are a few studies suggesting a suboptimal cortisol response to ACTH stimulation test in children (1-4) and adults (5-7) with NCCAH.
- The clinical significance of this finding is not clear, since the majority of patients with NCCAH and inadequate cortisol response do not exhibit signs of adrenal insufficiency (1,7).

- The **objective** of the study was to evaluate cortisol response to corticotropin (ACTH) stimulation test in children and adolescents with NCCAH and heterozygosity for CYP21 gene molecular defects with clinical hyperandrogenism compared to children and adolescents with clinical hyperandrogenism and normal response to ACTH stimulation test.

METHODS

- Retrospective study
- 146 children and adolescents (26 boys and 120 girls) aged 0.7 – 17.5 years
  - 132 children (21 boys and 111girls), mean age was 7.26 (0.7-11.03) yrs with clinical signs of androgen excess
    - ➢clitoromegaly
    - ➢hyperpigmentation of external genitalia,
    - ➢advanced bone age,
    - ➢early growth of pubic or axillary hair,
    - ➢increased axillary body odor,
    - ➢acne
  - 14 adolescents (5 boys and 9 girls) with a mean age of 13.75 (11.3-17.5) yrs, who presented with
    - ➢hirsutism,
    - ➢intense acne
    - ➢and/or abnormal menses
- All subjects underwent an ACTH stimulation test
  - ➢85 subjects (76 children and 9 adolescents), mean age 8.2 (0.7-16.32) yrs with a normal response to ACTH stimulation test according to the 17OHP nomogram
  - ➢28 children and 3 adolescent girls with NCCAH, confirmed by genotyping All showed a peak 17-OHP level ≥ 16.2 ng/ml
  - ➢27 children and 3 adolescents with mutations in the CYP21A2 gene detected in one allele, designated as heterozygotes They all had 60min stimulated 17OHP level ≥3.35ng/ml

- 17OHP was determined by MicroElisa
- The Southern blot technique was employed for the detection of large deletions and conversions of the CYP21 gene
- Cortisol was determined by electrochemiluminescence immunoassay "ECLIA"

RESULTS

Table 1. Comparison among normal responders, heterozygotes and NCCAH subjects.

	Normal responders (n=85)	Heterozygotes (n=30)	NCCAH (n=31)	p-value
Sex (M/F)	14/71	3/27	9/22	0.13*
Tanner I/II-V	76/9	27/3	28/3	0.98*
	Mean (sd, range)			
Age (yrs)	8.19 (2.6) 0.7-16.32 a vs b, **p=0.018	7.1 (3.1) 0.95-14.24 b vs c, **p=0.47	7.65 (2.3) 3.34-17.5 a vs c, ** p=0.059	0.024***
17-OHP 0'	0.94 (0.3) 0.5-1.91 a vs b, **p=0.001	1.95 (1.9) 0.8-6.5 b vs c, ** p=0.000	16.31 (17.7) 1.34-65.0 a vs c, ** p=0.000	0.000***
17-OHP 60'	2.64 (0.6) (0.99-4.04) a vs b, **p=0.000	7.82 (3.8) (3.35-15.5) b vs c, ** p=0.000	47.05(24.4) (16.2-90.6) a vs c, p=0.000	0.000***
Cortisol 0'	14.04 (7.6) 2.97-34.8 a vs b, **p=0.73	14.67 (8.2) 5.43-40.89 b vs c, ** p=0.629	15.75 (10.1) 5.83-59.6 a vs c, ** p=0.445	0.721***
Cortisol 60'	34.92 (6.8) 19.91-46.68 a vs b, ** p=0.92	35.22 (8.9) 17.47-52.37 b vs c, ** p=0.001	28.34 (13.0) 12.25-84.40 a vs c, ** p=0.000	0.000***

*:chi-square test, **: MannWhitney, ***: Kruskall Wallis
a:normal responders, b: heterozygotes, c: NCCAH

Table 2. Subjects with impaired cortisol response to ACTH stimulation test

Patient No	Sex	Age (yrs)	Cortisol 0' (μg/dl)	Peak Cortisol	17OHP 0' (ng/ml)	17OHP 60'	Genotype	
1	F	17.5	13.48	15.62	46.25	50.5	p.V281L/DELETION	NCCAH
2	F	6.9	10.75	12.25	50.6	90.6	p.P30L/p.P30L	NCCAH
3	F	7.59	9.71	16.63	15.5	78.4	p.P281L/p.Q318X	NCCAH
4	F	6.14	16.87	17.91	57.5	75.0	p.P30L/p.V281L	NCCAH
5	F	7.01	9.92	17.17	14.9	84.0	I2splice/p.PV281L	NCCAH
6	F	7.77	9.72	14.38	15.25	71.5	p.V281L/p.V281L	NCCAH
7	F	6.59	14.88	17.29	30.5	80.0	p.P30L/p.P30L	NCCAH
8	F	16.5	9.37	17.47	1.23	11.9	p.P30L/N	HETEROZYGOTE

Table 3. Comparison of 17OHP basal and stimulated levels between NCCAH subjects with impaired and NCCAH subjects with adequate cortisol response to ACTH test

Response to cortisol	Sex (M/F)	Age (yrs)	17OHP 0' (ng/ml)	17OHP 60' (ng/ml)	Cortisol 0' (μg/dl)	Cortisol 60' (μg/dl)
			Mean (sd) range			
Impaired (n=7)	0/7	8.5 (4.0) 6.14-17.5	32.92(18.4) 14.9-57.5	75.72(12.7) 50.55-90.6	12.2(2.8) 9.71-16.87	15.83(2.1) 12.25-17.91
Adequate (n=24)	9/17	7.82(2.6) 3.34-13.78	11.46(14.5) 1.34-65.0	38.69(20.3) 16.2-87.4	16.8(11.3) 5.83-59.6	31.99(12.6) 20.86-84.4
p-value	0.054	1.0*	0.000*	0.000*	0.444*	0.000*

*Mann-Whitney, ** chi-square test

CONCLUSIONS

- Our study reports an impaired cortisol response to ACTH stimulation test in children and adolescents with NCCAH, with approximately one fifth of subjects exhibiting a suboptimal cortisol response to ACTH stimulation.
- Children with NCCAH and impaired cortisol response had higher basal and stimulated 17OHP levels compared to the rest of NCCAH children
- The findings of the study are of clinical importance since not all NCCAH children/adolescents receive hydrocortisone treatment. Therapy for NCCAH children and adolescents needs to be individualized. The initiation and/or discontinuation of treatment in patients with suboptimal cortisol response deserves additional consideration.

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