Central adrenal insufficiency is not a common feature in CHARGE syndrome

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Background

CHARGE syndrome (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital hypoplasia, and Ear abnormalities) is caused by a mutation in the CHD7 gene. CHARGE syndrome shares features with Prader-Willi syndrome, especially regarding hypothalamic-pituitary abnormalities. In Prader-Willi syndrome, central adrenal insufficiency (CAI) during stressful conditions has been described. The presence of CAI in CHARGE syndrome has never been studied, although unexpected mortality has been observed.

Objective

The aim of our study was to assess the presence of CAI in children with CHARGE syndrome.

Patients and Methods

Patients (aged 20 months to 18 years) with genetically confirmed CHARGE syndrome were recruited from our national CHARGE clinic. To detect CAI, a low-dose ACTH test (LDAT) (0.5 µg/1.73 m2 body surface area Synacthen®) was performed. Blood samples were taken at -15, 0, 30, and 60 minutes. A maximum cortisol concentration > 500 nmol/l excluded CAI.
In case of suspected CAI, a glucagon test (0.05 - 0.1 mg glucagon per kg body weight, maximum 1 mg) was performed on a separate occasion. Blood samples were taken at baseline and then every 30 minutes during 3 consecutive hours. Cut-off cortisol levels to detect CAI were similar as in the LDAT.

Results

- From 83 eligible patients, 27 were included in the study. In 3 patients, the LDAT could not be performed due to technical reasons, and 1 patient withdrew from the study.
- The 23 tested patients (14 males) had a mean (SD) age of 9.3 (5.0) years.
- Seven patients had an insufficient maximum cortisol concentration in the LDAT (mean (SD) 425 (71) nmol/l), and underwent a glucagon test (1 patient underwent a standard dose ACTH test).
- One of these 7 patients was diagnosed with CAI (maximum cortisol concentration 415 nmol/l).

Conclusion

CAI is not a common feature in CHARGE syndrome. Further studies in a larger number of patients are required to confirm our findings.

Characteristics of the children with CHARGE syndrome.

Patient	Age *years*	Sex	*CHD7* Mutation	ACTH LDAT *ng/l*	Maximum cortisol LDAT *nmol/l*	Maximum cortisol GST *nmol/l*
1	14,9	F	missense	29	605	n/a
2	8,3	M	nonsense	25	485	510
3	3,8	F	splice site	14	525	n/a
4	13,8	M	splice site	22	380	415
5	16,9	M	splice site	20	430	510
6	11,6	F	splice site	7,1	585	n/a
7	3,2	M	splice site	44	620	n/a
8	2,3	F	nonsense	22	645	n/a
9	13,5	M	nonsense	2,8	475	690
10	5,9	F	frame shift	15	470	713*
11	5,8	M	nonsense	74	685	n/a
12	6,6	M	frame shift	16	650	n/a
13	14,4	F	nonsense	30	610	n/a
14	15,5	M	frame shift	23	450	610
15	2,9	M	frame shift	15	625	n/a
16	1,9	F	frame shift	23	765	n/a
17	14,9	M	splice site	21	595	n/a
18	8,4	M	frame shift	22	525	n/a
19	14,9	F	nonsense	5,4	625	n/a
20	8,1	M	frame shift	30	510	n/a
21	4,1	M	nonsense	12	285	600
22	11,8	M	splice site	95	677	n/a
23	10,7	F	nonsense	17	649	n/a

*Patient underwent standard dose ACTH test instead of glucagon stimulation test
F, female; GST, glucagon stimulation test; LDAT, low dose ACTH test; M, male; n/a, not applicable

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