Serum cortisol and cortisone ratio as sensitive tool to identify subjects with severe or partial 11β-hydroxysteroid dehydrogenase type 2 deficiency

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Background

Severe deficiency of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) triggers activation of mineralocorticoid receptor (MR) by cortisol and causing apparent mineralocorticoid excess (AME) syndrome characterized mostly by low-renin arterial hypertension and hypokalemia. AME subjects and first degree relatives could give us clues about the biochemical presentation of partial deficiencies of 11BHSD2. In Chile, we have found two pediatric patients with AME, associating the D223N (rs121917833) and R213C mutations.

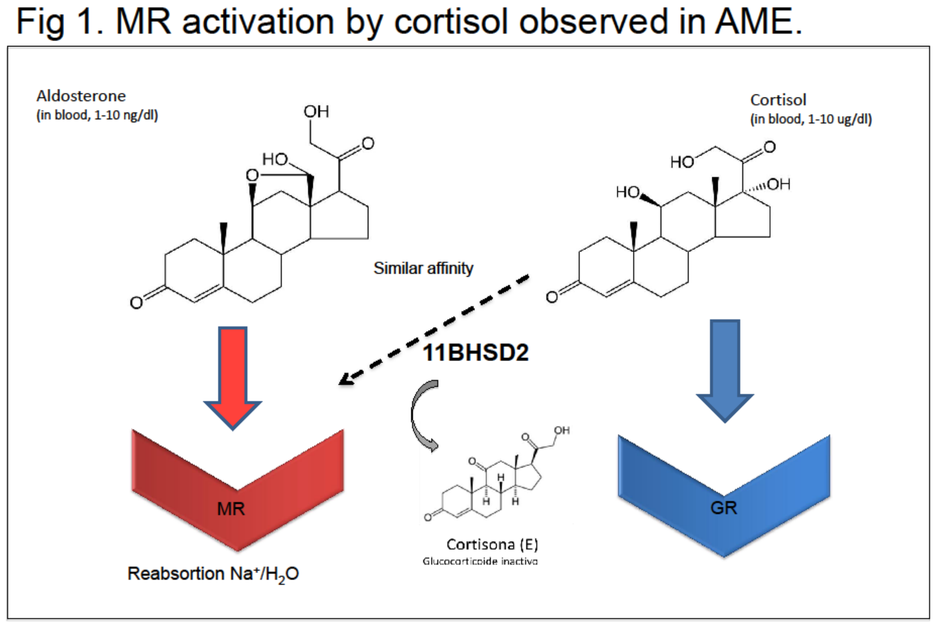
Aim

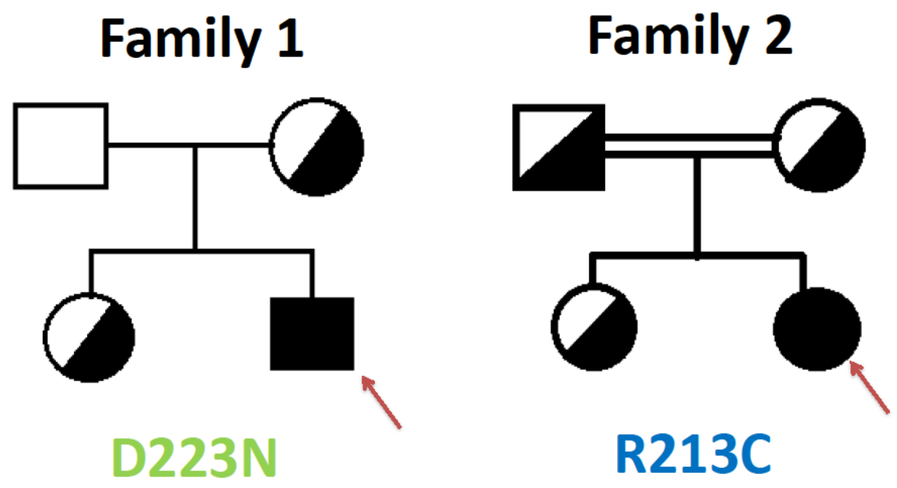
To study the current clinical and biochemical status of 2 patient with AME including their first degree relatives, and to evaluate serum cortisol/cortisone as a biomarker of partial 11βHSD2 deficiency.

Subjects and Methods

We have recently evaluated 2 AME patients and their families. In all of them, we measured serum potassium, aldosterone and plasma renin activity (PRA). Serum cortisol (F) and cortisone (E) were measured by LC-MS/MS, and F/E ratio was calculated. Genetic analyses of HSD11B2 gene were performed by PCR-HRM and DNA-sequencing.

Fig 1. MR activation by cortisol observed in AME.





Results

Case (1): Male patient with the **D223N** mutation in HSD11B2, 17 y-old, HT (165/110mmHg), BMI 22,6 Kg/m2 (p69), K+ (2,1 mEq/L), aldosterone (1ng/dL), PRA (<0,2ng/ml*h) and a high F/E ratio (28.8 [RV: 1.63-5.15]). His sister and mother are heterozygous for D223N. They are normotensives and do not show biochemical abnormalities, but a high F/E ratio (Both in percentil p97).

Case (2): Female Patient with the **R213C** mutation in HSD11B2, 2 y-old, HT (197/133mmHg), K+ (2,9mEq/L), aldosterone (1ng/dL) , PRA (<0,2 ng/ml*h) and a high F/E ratio (175 [RV: 1.63-5.15]). Her father, mother and sister are heterozygous for R123C. Their clinical and biochemical parameters are mostly normal, but with a high F/E ratio E (percentil p92, p93 and p85,

	Index case D223N	Mother	Sister	Reference values
Age (years-old)	17	33	9	
DBP (mmHg)	165	110	90	
SBP (mmHg)	110	70	60	
BMI (Kg/m2)	22,6 (p69)	29,9	18,1(p84)	
K+ (mEq/L)	2,1	3,7	3,8	[3.5 – 5]
Aldosterone (ng/dL)	1,0	3,8	13,9	[1.8 – 23.2]
PRA (ng/mL*Hr)	<0,2	2,6	4,6	[1,3 – 4]
Cortisol (ug/dL)	13,3	26,3	13,3	Adults [4,21 – 21,2] Children [4,1 – 11,8]
Cortisone (ug/dL)	0,46	2,0 (p29)	2,2 (p18)	Adults [1,38 – 3,33] Children [1,74 – 3,84]
F/E ratio	28.8 (>>p99)	13,2 (>p97)	6,0 (>p97)	Adults [2,58 – 7,8] Children [1,63 - 5,15]

	Index case R213C	Mother	Father	Sister	Reference values
Age (years-old)	2	34	36		
DBP (mmHg)	197	124	150	110	
SBP (mmHg)	133	68	75	60	
BMI (Kg/m2)	13,5 (p3)	31	28,6	16.9 (p78)	
K+ (mEq/L)	2,9	4,2	3,7	4,4	[3.5 – 5]
Aldosterone (ng/dL)	1,0	4,8	8,5	8,0	[1.8 – 23.2]
PRA (ng/mL*Hr)	<0,2	2,04	12,8	1,85	[1,3 – 4]
Cortisol (ug/dL)	19,7	13,7	13,95	7,34	Adults [4,21 – 21,2] Children [4,1 – 11,8]
Cortisone (ug/dL)	0,11	1,96(p25)	2,13 (p30)	1,71 (p2,5)	Adults [1,38 – 3,33] Children [1,74 – 3,84]
F/E ratio	175 (>>p99)	6,99 (p93)	6,55 (p92)	4,29 (p85)	Adults [2,58 – 7,8] Children [1,63 - 5,15]

Discussion

Clinical and biochemical findings in AME patients and their families support that high serum cortisol/cortisone ratio (>p90), in general associated to serum cortisone levels (<p30), could be a sensitive tool to identify biochemically subjects with severe or partial 11βHSD2 deficiency, independent to a low-renin hypertension, low aldosterone or hipokalemia condition. Other complementary biomarkers are necessary to evaluate the progression of this condition.

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