GLUCOCORTICOID RESISTANCE SYNDROME – CASE REPORT

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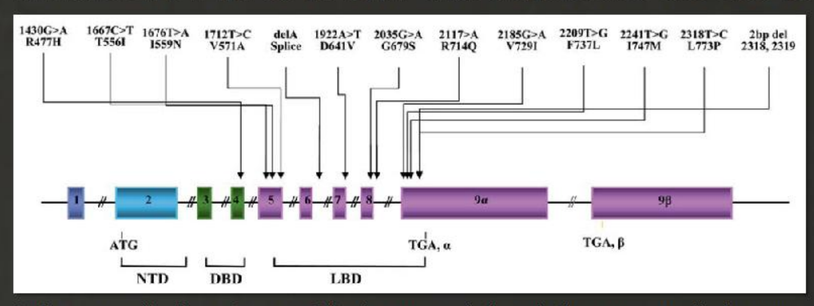
INTRODUCTION

Glucocorticoid Resistance Syndrome (GRS) or Chrousos Syndrome is a rare familial or sporadic genetic condition, caused by mutations in the glucocorticoid receptor gene (GR). It is characterized by parcial resistance of target tissues to cortisol action and subsequent activation of hypothalamus-pituitary-adrenal axis with compensatory elevation of ACTH that stimulates adrenal glands to hypersecretion of cortisol, mineralocorticoids and androgens. Clinical spectrum is very wide, varying from assymptomatic cases that only present laboratorial alterations to more severe forms with arterial hypertension (AHT), metabolic alcalosis, hypokaliaemia and virilization. Low levels of renin and aldosterone are due to inappropiate activation of mineralocorticoid receptors by cortisol in excess.

Currently, at least 17 inactivating mutations in exons 4-9 of NR3C1 gene, occurring in the ligand-binding domain and DNA-binding domain of GR a-isoform, have been described as the cause of GRS. Most of these induce glucocorticoid resistance through more than one defect in the signal transduction cascade of glucocorticoids, which results in impaired transcription of glucocorticoid responsive genes.



Ilust. 1 – Localization of some of the known mutations in the GR gene that cause GRS.
From: *print screen* in E. Charmandaria, "Primary Generalized Glucorticoid Resistance and Hypersensitivity", Hormone Research Paediatrics, 2011;76:145–155

CASE REPORT

C.N.S.A. ♂, 19 years-old (yo), black, parcially autonomous, born and resident in Cape Verde

Previous Medical History:
- ✓ Delivery at term, eutocic
- • Delayed psychomotor development
- • Epilepsy diagnosed at 6 yo, treated with Carbamazepine until 14 yo, with no further convulsive episodes
- • AHT diagnosed at 14 yo
- ✓ Normal puberty at adequate age

Medication:
Nifedipine 20 mg/day; Atenolol 50 mg/dia

Family History:
- ▪ Maternal grandmother – AHT
- ▪ Paternal half-brother – Epilepsy, died from infeccious disease (?)

Cape Verde:

	Nov/2010	Apr/2012
ACTH pg/ml (ND-46)	**111**	**121**
Cortisol µg/dl (5-25)	17,2	
Noradrenaline (12-869)	9	15
Adrenaline (2-22)	4	1

August/2013:
Referred to ENDOCRINOLOGY for:
AHT + ACTH ↑

Endocrinology Department in CCH:

Physical Examination:
- ✓ Height 1,70m Weight 52 kg BMI 18
- ✓ BP 139/95 mmHg
- ✓ No features of Cushing Syndrome
- ✓ Normal adult secondary sexual development
- ✓ Body hair distribution adequate for age and sex
- ✓ No signs of hipervirilization
- ✓ Palpable and wide femural pulses

Laboratorial Evaluation	
ACTH pg/ml (ND-46)	**158**
Cortisol 8h/0h µg/dl (5-25)	21,9/1,8
Cortisol U 24h µg/day (20-90)	**102,5**
Cortisol after-1 mg Dx µg/dl	**10,2**
Active Renine µUI/ml (4,4-46,1)	**1,4**
Aldosterone ng/dl (4-31)	**<1,1**
Aldosterone U24h µg/day	0,9
Normetanefrines µg/day (35-445)	405,5
Metanefrines µg/day (25-312)	243
17-OH-Progesterone ng/ml (0,6-3,4)	**4,82**
11-Desoxicortisol ng/ml (<8)	2,93
Microalbuminuria µg/mg	**95,1**

FUNCTIONAL TESTS	ACTH pg/ml	Cortisol µg/dl	Cortisol U24h µg/day
Low-dose Dx	130	**19,8**	23
High-dose Dx	24,5	<1,0	11,9

- ➢ **Biochemical study suggestive of *endogenous hypercortisolism*, with preservation of the circadian rhythm of cortisol secretion**
- ➢ **No clinical features of hypercortisolism**
- ➢ **AHT**

Glucocorticoid Resistance Syndrome?

GENETIC STUDY:
Frameshift mutation c.2159_2160delAA, in heterozigoty in the NR3C1 gene
Not yet described in the literature or data base

Cranial-CT 30/12/2011
- • No occuptying space lesions, bleeding or isquemia.

Abdominal-CT 30/12/2011
- • Adrenal glands with normal size and morfology, without nodular lesions or other significant alterations.

Abdominal/ Renal US 07/12/2009
- • Without any hepato-bilio-pancreatic alterations. Both kidneys with normal size and position.Normal adrenal glands.

Renal Angio-TC Sept/2013
- • No alterations suggestive of renal arteries stenosis.

Pituitary MRI Sept/2013
- • No patologic features in sellar region. Slight left deviation of pituitary stalk lateral without any direct or indirect signs of microadenoma

Echocardiogram Aug/2013
- • Preserved sistolic function. Normal left ventricule. Abnormal movement of mitral valve chordae tendinae, with diastolic opening typical of rheumatic disease in the past. The opening is wide and without hemodynamic consequences.

- ✓ Probably pathogenic mutation.
- ✓ The deletion is predicted to introduce a premature "stop" codon, which results in a truncated protein with the loss of 6% of amino acids.
- ✓ Genetic study of relatives has not been done yet, since they live abrod.

❑ Anti-hypertensive medication was withdrawn and spironolactone was started resulting in hyperkalaemia without blood pressure control. The patient was discharged with the previous treatment.

CONCLUSIONS

Diagnosis of GRS is suggested by the finding of persistant elevated urinary cortisol in a young man with AHT without any other features of Cushing Syndrome. The elevation of cortisol and androgens, as well as the resistance to dexamethasone supression depend on the severity of the defect in the signal transduction of glucocorticoids. A novel frameshift mutation in the gene NR3C1 responsible for GRS was identified in this patient. Further molecular and genetic studies of the patient and relatives are expected to be performed in order to identify the transduction defect involved and whether it is an inherited or *de novo* mutation.

17 ECE
1222--EP
Clinical Cases Pituitary/Adrenal
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DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16–20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY
PosterSessionOnline.com