55th Annual ESPE Meeting
ESPE 2016 10-12 SEPTEMBER PARIS, FRANCE
Horizons in Paediatric Endocrinology

TRANSIENT GENERALIZED GLUCOCORTICOID HYPERSENSITIVITY SYNDROME

Eleni Magdalini Kyritsi[1], Nicolas C. Nicolaides[1,2], Agaristi Lamprokostopoulou[2], Athina Xaidara[1], Elizabeth Georgiadou[1], Vassiliki Dimitropoulou[1], Alketa Stefa[2], Amalia Sertedaki [1], George P. Chrousos [1,2], Evangelia Charmandari[1,2]

[1]Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece;
[2]Division of Endocrinology and Metabolism, Clinical Research Center, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

The authors have no financial relationship(s) to disclose relevant to this poster presentation

BACKGROUND

Transient Generalized Glucocorticoid Hypersensitivity (TGGH) is a rare disorder characterized by increased tissue sensitivity to glucocorticoids and compensatory hypoactivation of the hypothalamic-pituitary-adrenal (HPA) axis. The condition itself and the underlying molecular mechanisms have not been fully elucidated.

OBJECTIVE AND HYPOTHESES

To present the clinical manifestations, endocrinologic evaluation and molecular studies in a patient with TGGH.

METHOD AND RESULTS

A 14-year old boy presented with a 9-month history of clinical manifestations suggestive of Cushing syndrome (Fig 1A).
Endocrinologic evaluation revealed low 08:00h plasma ACTH (1 pg/mL), serum cortisol (0.08 μg/dL) and 24h-urinary free cortisol (UFC) concentrations (2.75 μg/24h) (Table 1). The oral glucose tolerance test (OGTT) indicated severe insulin resistance and hyperinsulinemia. Moreover, HbA1c levels were elevated (6.1%).
Screening for synthetic glucocorticoids in both serum and urine samples was negative (Table 2). Following stimulation with oCRH (1 μg/Kg), ACTH concentrations increased significantly, while the response of cortisol was suboptimal for the degree of post-CRH ACTH elevation (Table 3).

Table 3. CRH test during the active phase of the disease (100 μg iv)

min	-15	0	15	30	45	60	90	120
Cortisol (μg/dL)	12,88	10,23	15,54	***17,94***	***19,43***	16,89	10,13	7,4
ACTH (pg/mL)	35,41	30,91	***108,2***	***94,52***	71,91	49,84	26,04	20,04

Sequencing of the human glucocorticoid receptor (hGR) gene revealed no mutations or polymorphisms. Serological tests revealed elevated HSV-6 IgG titers (1/320) (Table 4). The dexamethasone-binding assays demonstrated increased affinity of the patient's hGR receptor for the ligand compared with a control subject matched for sex, age and body mass index (Kd=5.7 ± 2.65 nM vs. 14.7 ± 5.3 nM) (Figure 2).
The clinical manifestations of the disease gradually resolved over the ensuing 5 months (Fig 1B). Plasma ACTH, serum cortisol and 24h-UFC concentrations normalized (ACTH: 35.27 pg/mL, cortisol: 11.02 μg/dL, 24h-UFC: 55.57 μg/24h). Following OGTT, serum insulin concentrations remained persistently elevated, however, the HbA1c levels were normal (5.5%). The repeat dexamethasone-binding assays showed that the patient's hGR receptor had similar affinity for the ligand, compared with the control subject (Kd=17,6 ± 0,0 nM vs. Kd=14.7 ± 5.3 nM).

CONCLUSION

Our results suggest that a transient postreceptor defect may have enhanced glucocorticoid signal transduction, leading to TGGH.

Table 1. Endocrinologic investigations during the active phase of the disease

	Result	Ref. range
T4 (μg/dL)	6,7	4,5-12,5
TSH (μIU/mL)	2,78	0,3-5,0
FSH (mIU/mL)	7,3	1,5-12,4
LH (mIU/mL)	2,1	1,7-8,6
PRL (ng/mL)	7,9	3-18
Aldosterone (pg/mL)	154	25-445
Renin (μIU/mL)	29,1	4-50
Testosterone (ng/mL)	1,7	0,8-9,0
DHEA-S (μg/dL)	***15,0***	70,2-492
ACTH (pg/mL)	***1***	7-64
Cortisol (μg/dL)	***0,08***	6,2-19,4
24h UFC (μg/24h)	***1,99/2,75***	4-176
Insulin (μIU/mL)	***27,2***	2,6-25
IGF-1 (ng/mL)	411	202-957

Table 2. Synthetic glucocorticoid Screen, Serum and Urine (LC-MS/MS)

	Result
Betamethasone	Negative
Budesonide	Negative
Dexamethasone	Negative
Fludrocortisone	Negative
Fluticasone proprionate	Negative
Megestrol Acetate	Negative
Methylprednisolone	Negative
Prednisolone	Negative
Prednisone	Negative
Triamcinolone Acetonide	Negative

Table 4. Serological tests during the active phase of the disease

Blood test	Result
HSV 6 IgG	***320***
Adenoviral IgG, IgM	IgM (-), low IgG titers
Coxiella burnettii IgG, IgM, Rickettsia conorii IgG, IgM Rickettsia mooseri/typhi IgG, IgM, Parvovirus B19 IgM, IgG, IgG HSV-1, IgG HSV-2, IgM HSV (1+2) anti-EBNA, EA-IgG, VCA-IgM, VCA-IgG, anti-HTLV I+II	Negative
Borrelia burgdorferi Flagellin, p 41 IgG, IgM	Positive (protein of low specificity)

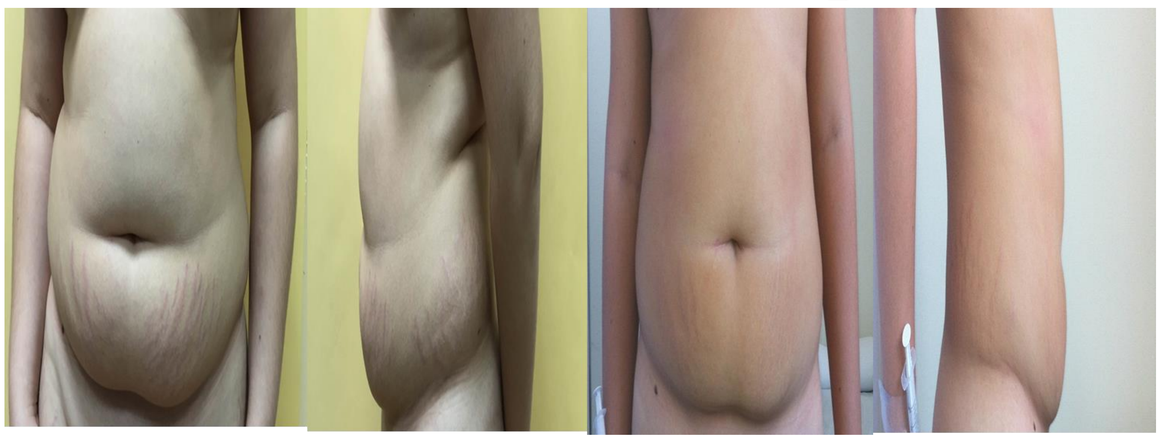

Figure 1. Patient at presentation with Cushingoid phenotype (A) and at follow-up visit after 5 months (B)

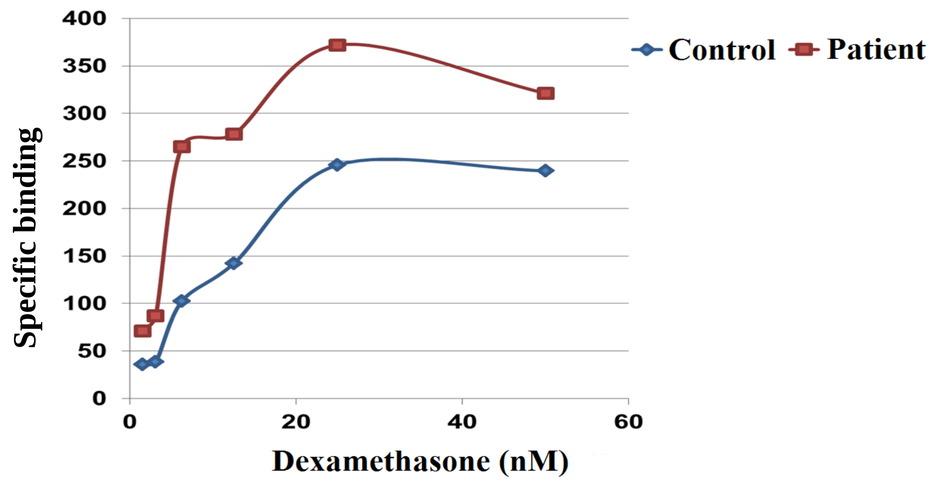

Figure 2. Dexamethasone-binding assays in the acute phase. Compared with the control subject, the patient's hGR receptor demonstrated increased affinity for the ligand (Kd=5.7 ± 2.65 nM vs. 14.7 ± 5.3 nM)

References

1. Charmandari E, Kino T, Chrousos GP. Endocr Dev. 2013;24:67-85
2. Charmandari E. Horm Res Paediatr. 2011;76(3):145-55
3. Charmandari E et al. J Clin Endocrinol Metab. 2008 Dec;93(12):4963-8

DOI: 10.3252/pso.eu.55ESPE.2016