AACE Clinical Case Rep. 7 (2021) 367–371

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

A Case of Glucocorticoid Hypersensitivity Syndrome Associated With Underlying Rubella Virus Infection

Zhen Zhang, MS, Ying Feng, PhD, Yang Cao, PhD, Yan Chen, MS, Fangping Li, PhD *

Department of Endocrinology, The Seventh Affiliated Hospital, Sun Yat-sen University, China

ARTICLE INFO

Article history:
Received 21 January 2021
Received in revised form
14 May 2021
Accepted 15 June 2021
Available online 23 June 2021

Key words:
Cushing syndrome
glucocorticoid hypersensitivity
hypocortisolemia
rubella virus
case report

ABSTRACT

Objective: The objective of this article is to report a rare case of glucocorticoid hypersensitivity syndrome, which may be associated with an underlying rubella virus infection.
Case Report: A 29-year-old man showed progressive weight gain for 16 months accompanied by a moon face, enlarged dorsocervical fat pad, central obesity, and purple striae. His cortisol circadian rhythm was normal, and plasma cortisol levels at 8:00 AM fluctuated between 3.2 and 9.54 μg/dL (reference range, 4.3-22.4 μg/dL). A dexamethasone suppression test with a very low dose (0.25 mg) of dexamethasone showed a marked decrease in plasma cortisol level to 0 μg/dL. Adrenal computed tomography and pituitary magnetic resonance imaging findings were normal. The Z-score of the bone density in the lumbar spine was −4.2. The IgM antibody for the rubella virus was positive. His erythrocyte sedimentation rate was 24 mm/hour (reference range, <15 mm/hour), and the C-reactive protein level was 9.22 mg/L (reference range, <5 mg/L). After 3 months, his symptoms resolved spontaneously. The erythrocyte sedimentation rate and C-reactive protein level returned to normal. The IgM antibody for the rubella virus turned negative, whereas the IgG antibody for the rubella virus was positive.
Discussion: According to the paradox between clinical manifestations and laboratory tests exogenous Cushing syndrome, cyclical Cushing syndrome, and glucocorticoid hypersensitivity syndrome all should be considered in the diagnosis. Detailed medical history inquiry, complete endocrine hormone testing, and continuous follow-up are all critical for diagnosis.
Conclusion: Consequently, the patient was diagnosed with glucocorticoid hypersensitivity syndrome. This case illustrates the need to consider the possibility of glucocorticoid hypersensitivity syndrome in a patient who has the manifestations of Cushing syndrome but paradoxical hypocortisolemia, especially after rubella virus infection.

Introduction

Glucocorticoid hypersensitivity syndrome is a rare endocrinologic condition caused by cell hypersensitivity to glucocorticoids. Iida et al[1] first described this disease in 1990. To date, only a few cases of glucocorticoid hypersensitivity syndrome have been reported in the literature. Patients diagnosed with this disease have typical clinical manifestations of Cushing syndrome, but the level of endogenous glucocorticoids is normal or even decreased.

A clear diagnostic criterion for glucocorticoid hypersensitivity syndrome has not yet been established. Before the diagnosis of glucocorticoid hypersensitivity syndrome, iatrogenic Cushing syndrome and surreptitious self-medication must be ruled out, which can lead to Cushing syndrome and paradoxical hypocortisolemia. Therefore, repeated and detailed medication history inquiry is very important, including asking whether the patient has taken traditional Chinese medicines and health care products and whether relatives and friends have autoimmune disorders. Cyclical Cushing syndrome also needs to be ruled out. Therefore, cortisol levels should be measured multiple times at different times. In addition, it is required to exclude the presence of clinical conditions associated with a decrease in corticosteroid-binding globulin level, in which despite low total cortisol levels, the level of its free fraction remains within the normal limit.[2] Apart from typical cushingoid symptoms in the presence of low or normal serum cortisol level, a

Abbreviations: ESR, erythrocyte sedimentation rate; hGR, human glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal.

* Address correspondence to Dr Fangping Li, Department of Endocrinology, The Seventh Affiliated Hospital, Sun Yat-sen University, No. 628, Zhenyuan Road, Guangming District, Shenzhen, Guangdong, China.
E-mail address: zhenmiaomiao1986@163.com (F. Li).

https://doi.org/10.1016/j.aace.2021.06.010

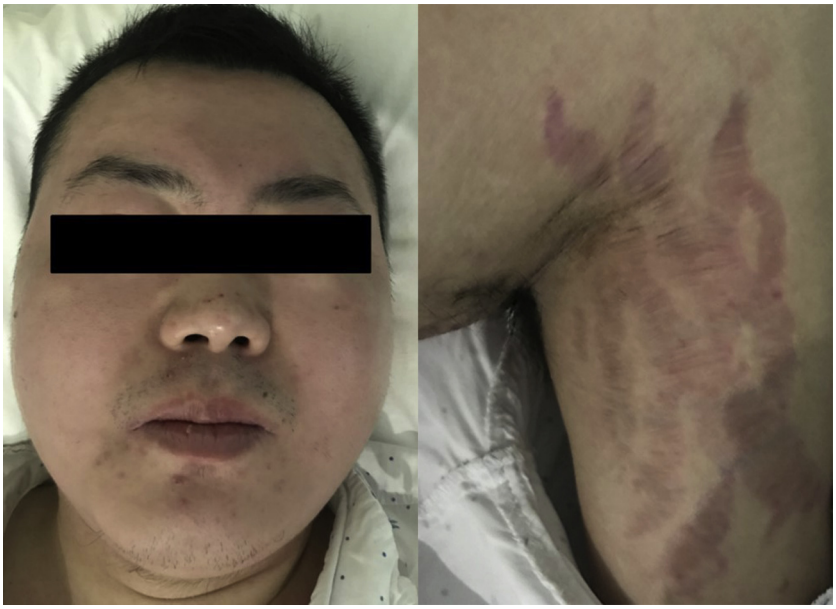

Fig. 1. Moon face and purple striae.

dexamethasone suppression test with a very low dose (0.25 mg) of dexamethasone can lead to a marked decrease in plasma cortisol level,[3] and the corticotropin-releasing hormone and Synacthen stimulation tests show a poor response of adrenocorticotropic hormone (ACTH) and cortisol in a patient with glucocorticoid hypersensitivity syndrome.[4] Moreover, some in vitro experiments have been performed to diagnose this disease. For example, it can be diagnosed by measuring the sensitivity of cultured skin fibroblasts to dexamethasone in vitro.[5] Thymidine incorporation and dexamethasone-binding assays on peripheral blood mononuclear cells in association with the sequencing of the human glucocorticoid receptor (hGR) gene are also important methods to confirm the diagnosis.[6,7]

Here, we report a case of glucocorticoid hypersensitivity syndrome, present the clinical manifestations and endocrinologic evaluation, and discuss its etiology.

Case Report

A 29-year-old man presented with a history of progressive weight gain, accompanied by the development of acne on the face and violaceous striae on the armpits and thighs since December 2018. Over the last 16 months, his body weight increased by 5 kg. In July 2019, he had weakness in both lower limbs, and his blood potassium level was 3.0 mmol/L. After potassium supplementation, his muscle strength recovered, and the blood potassium level returned to 3.8 mmol/L. Without obvious causes, he had back pain and suffered compression fractures of the thoracic and lumbar vertebrae in January and March 2020, respectively. He was in good health before and had no history of smoking or drinking. His father died of esophageal cancer 1 year ago, and his mother and two brothers are in good health. He is mentally healthy and cooperative during hospitalization. After repeated inquiries and checking his medical records, we learned that he did not take any medicines and health care products before the onset of illness.

On admission, his blood pressure was 151/100 mm Hg, his height was 166 cm, his weight was 68.5 kg, and his body mass index was 24.9 kg/m^2. Physical examination revealed a moon face with acne, enlarged dorsocervical fat pad, central obesity, and thin skin with wide purple striae on both sides of the armpits and inner thighs (Fig. 1).

Table 1
Cortisol and ACTH Tests of the Patient in Different Days and Times

Date	Time	Cortisol (μg/dL)	ACTH (pmol/L)
15 Apr	8 AM	8.07	6.17
	4 PM	6.92	5.91
	0 AM	2.08	3.08
21 Apr	8 AM	9.54	9.56
	4 PM	2.98	2.64
	0 AM	0.56	1.76
18 Jun	8 AM	3.2 ↓	5.6
03 Jul	8 AM	4.1 ↓	-
	4 PM	2.9	-
	0 AM	<0.8	-
14 Jul	8 AM	5.3	-
	4 PM	5.0	-
	0 AM	<0.8	-
05 Aug	8 AM	6.3	-
	4 PM	4.1	-
	8 AM	7.1	-
16 Sept	8 AM	7.1	-
	4 PM	5.7	-
	0 AM	<0.8	-
13 Dec	8 AM	4.01 ↓	4.55

Abbreviation: ACTH = adrenocorticotropic hormone.
Reference values of cortisol (8:00 AM): 4.3-22.4 μg/dL.
Reference values of ACTH (8:00 AM): 1.6-13.9 pmol/L.

The cortisol circadian rhythms on different days were tested and this showed that the patient had a normal cortisol circadian rhythm, and his morning (8:00 AM) cortisol levels were normal or decreased (Table 1). The 24-hour urinary free cortisol, 17-hydroxycorticosteroid, and 17-ketosteroid levels on two independent samples decreased (Table 2). His corticosteroid-binding globulin was 17.1 mg/L (reference range, 15-20 mg/L). The plasma dehydroepiandrosterone sulfate level was 101.30 μg/dL (reference range, 160-449 μg/dL). A 250-μg cosyntropin stimulation test showed a poor cortisol response with a peak cortisol level of 15.7 μg/dL (reference range, >18 μg/dL). The plasma renin activity was 1.68 ng/mL/hour (reference range, 0.15-2.33 ng/mL/hour),

Table 2
Twenty-Four-Hour Urinary UFC, 17-OHCS, and 17-KS

Date	UFC (μg/24 hours)	17-OHCS (mg/24 hours)	17-KS (mg/24 hours)	Urine volume (L)
15 Apr	<1.1↓	2.9 ↓	1.3 ↓	1.2
18 Jun	13.8	6.0	1.8 ↓	1.5

Abbreviations: UFC = urinary free cortisol; 17-OHCS = 17-hydroxycorticosteroid; 17-KS = 17-ketosteroid.
Reference values of UFC: 3.5-45 μg/24 hours.
Reference values of 17-OHCS: 6-25 mg/24 hours.
Reference values of 17-KS: 2-8 mg/24 hours.

Table 3
Thyroid Function

Parameters	Value	Reference range
TSH (uIU/mL)	0.91	0.35-4.94
FT3 (pg/mL)	3.03	1.71-3.71
FT4 (ng/dL)	1.13	0.70-1.48

Abbreviations: FT3 = free triiodothyroinine; FT4 = free throxine; TSH = thyroid-stimulating hormone.

Table 4
Testosterone, LH, FSH, and Prolactin Levels

Parameters	Value	Reference range
Testosterone (nmol/L)	26.94	4.94-32.01
LH (mIU/mL)	3.18	0.57-12.07
FSH (mIU/mL)	4.53	0.95-11.95
Prolactin (ng/mL)	21.04	3.46-19.4

Abbreviations: LH = luteinizing hormone; FSH = follicle-stimulating hormone.

Table 5
Oral Glucose Tolerance and Insulin Release Test in the Disease Active and Resolution Phases

	Time (h)	Glucose (mmol/L)	Insulin (uU/mL)
Disease active phase	0	4.61	2.1
	2	10.54 ↑	83.46
Disease resolution phase	0	4.0	7.93
	2	6.2	28.02

The blood glucose level in 2 hours of the oral glucose tolerance test in the disease active phase is higher than 7.8 mmol/L, indicating impaired glucose tolerance.

aldosterone level was 125.12 pg/mL (reference range, 10-160 pg/mL), and simultaneous potassium level was 3.86 mmol/L (reference range, 3.5-5.5 mmol/L). His thyroid function is shown in Table 3. His testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin levels are shown in Table 4. His growth hormone level was 1.58 ng/mL (reference range, 0.03-2.47 ng/mL). The oral glucose tolerance test suggested impaired glucose tolerance (Table 5). Bone metabolism markers are shown in Table 6. Adrenal computed tomography and pituitary magnetic resonance imaging did not reveal any abnormalities (Fig. 2 and 3). The bone density of the lumbar spine evaluated by a dual-energy X-ray bone densitometer showed the presence of severe osteoporosis (Z-score, −4.2). X-rays of the spine showed compression fractures of the 7th to 11th thoracic vertebrae and the 1st and 2nd lumbar vertebrae. The IgM antibody for the rubella virus was positive, and the erythrocyte sedimentation rate (ESR) and C-reactive protein level both increased (Table 7). Combined with the patient's clinical manifestations and examination results, glucocorticoid hypersensitivity syndrome was taken as a final diagnosis. In the following 3 months, the patient's symptoms resolved spontaneously. Although the patient's cortisol level was still lower than normal (Table 1), he had a weight loss of 5 kg, his moon face recovered, his blood pressure returned to normal (120-125/70-80 mm Hg), his glucose tolerance recovered (Table 5), and his bone density increased (Z-score, −1.5). Moreover, his ESR and C-reactive protein level also returned to normal (Table 7). The IgM antibody for the rubella virus was negative, whereas the IgG antibody for the rubella virus was positive.

Table 6
Bone Metabolism Markers

Parameters	Value	Reference range
Calcitonin (pg/mL)	3.86	< 6.4
25-Hydroxyvitamin D (ng/mL)	16.26	> 30
Parathyroid hormone (pg/mL)	29.9	15.0-68.3
Bone alkaline phosphatase (μg/L)	56.11	17.9-31.9

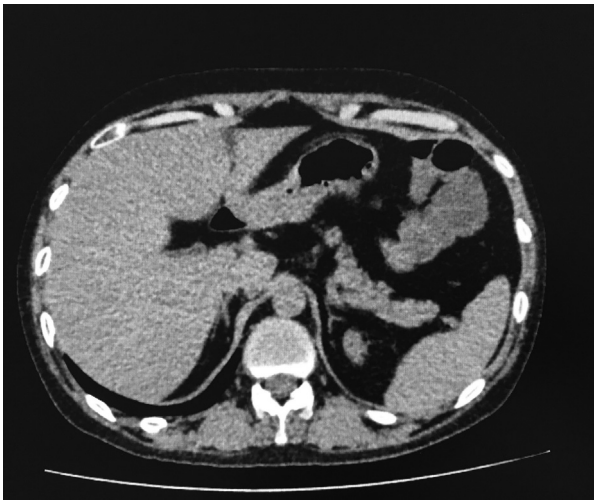

Fig. 2. Adrenal computed tomography image.

Discussion

In this case, we describe a patient who presented with typical clinical manifestations of Cushing syndrome including moon face, buffalo hump, central obesity, skin purple striae, hypertension, impaired glucose tolerance, hypokalemia, and pathologic fracture, but his plasma cortisol and ACTH levels were normal or decreased paradoxically. How can we explain this paradox?

Detailed inquiry and medical records revealed no history of exogenous glucocorticoid administration. Therefore, the possibility of exogenous Cushing syndrome was ruled out. At first, the diagnosis of cyclical Cushing syndrome was assumed. Cyclical Cushing syndrome is a pattern of hypercortisolism in which the biochemistry of cortisol production fluctuates rhythmically. Cortisol cycling has been defined as the presence of at least three peaks and two troughs of cortisol production.[8] However, after 7 months of follow-up, no cortisol peak was found in this patient. The patient's plasma cortisol was sustained at a low level. A poor response of cortisol to Synacthen stimulation indicated that the hypothalamic-pituitary-adrenal (HPA) axis in the patient was suppressed. Moreover, a marked decrease in plasma cortisol level caused by a dexamethasone suppression test with a very low dose of dexamethasone indicated that the sensitivity of the glucocorticoid receptor to glucocorticoid in this patient increased.[3] Although we did not perform any in vitro experiment, both the clinical picture and

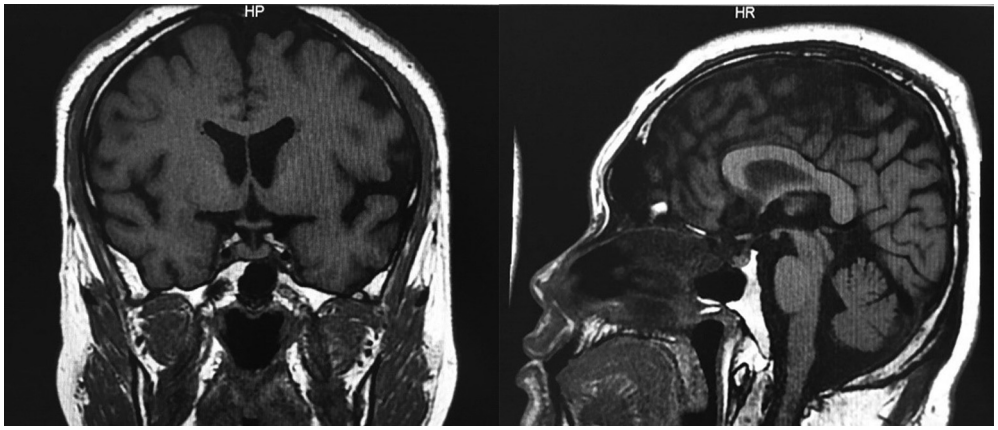

Fig. 3. Pituitary magnetic resonance image.

Table 7
ESR and CRP in the Disease Active and Resolution Phases

	ESR	CRP
Disease active phase	24	9.22
Disease resolution phase	8.4	1.5

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
Reference values of ESR: <15 mm/hour.
Reference values of CRP: <5 mg/L.

results of the endocrinologic evaluation were sufficient to establish the diagnosis of glucocorticoid hypersensitivity syndrome.

Although the patient's cortisol was suppressed, ACTH was still at a normal level. Plasma ACTH levels may be normal or low in primary generalized glucocorticoid hypersensitivity.[9] The reason why there is a lack of complete suppression of the HPA axis in glucocorticoid hypersensitivity remains unknown. Perhaps, it is because the patient's peripheral tissues are hypersensitive to cortisol; however, the sensitivity of glucocorticoids in the brain and pituitary is normal. Hypertension and hypokalemia are key features in this case. A case report also described a patient with cortisol hypersensitivity syndrome whose blood pressure was high.[5] The glucocorticoid receptor is widely expressed in a number of organ systems relevant to blood pressure regulation, including the kidney, brain, and vasculature. In the kidney, glucocorticoids can act on glucocorticoid receptors to promote renal sodium reabsorption. In vascular smooth muscle, studies have observed an upregulation in angiotensin II type I receptors induced by glucocorticoids, which are hypothesized to result in alterations in blood pressure. In the vascular endothelium, studies have suggested that glucocorticoids regulate vascular reactivity via suppression of the production of vasodilators, such as prostacyclin and nitric oxide, leading to hypertension.[10] Therefore, it is reasonable that cortisol hypersensitivity can cause high blood pressure. The cause of hypokalemia in this patient is still unknown. Glucocorticoids may also upregulate angiotensin II type I receptors in the kidney and cause hypokalemia.

The precise etiology of glucocorticoid hypersensitivity syndrome remains unknown. At the cellular level, the actions of glucocorticoids are mediated by the hGR, which is a member of the steroid hormone receptor family of the nuclear receptor superfamily of transcription factors. The mutations or polymorphisms in the hGR gene have been attributed to the molecular mechanism of glucocorticoid hypersensitivity syndrome, which increases the transcriptional activity of glucocorticoid-responsive genes.[9] However, to date, only one patient has been reported with manifestations of glucocorticoid hypersensitivity syndrome caused by a novel hGR gene mutation, which resulted in an aspartic acid (D) to histidine (H) substitution at amino acid position 401 in the amino-terminal domain of hGRα.[11] In addition to activating hGR gene mutations, N363S and BclI polymorphisms are associated with increased glucocorticoid sensitivity. Studies have found that the polymorphisms of N363S and BclI are associated with higher sensitivity to glucocorticoids in vivo, hypertension, visceral adiposity, elevated cholesterol and triglyceride levels, lower bone mineral density, and higher incidence of coronary artery disease.[12,13] Besides hGR gene mutations or polymorphisms, there have been a few cases with glucocorticoid hypersensitivity syndrome of no defect in the hGR gene.[1,4,5,6]

Whole-exome sequencing tests were performed and found no mutations or polymorphisms of the hGR gene in our case, including alpha or beta isoform. What is the mechanism leading to glucocorticoid hypersensitivity in our case? Nicolaides et al[14] reported a case of glucocorticoid hypersensitivity syndrome; a 9-year-old girl presented with an 8-month history of clinical manifestations suggestive of Cushing syndrome and paradoxically hypocortisolemia, whose symptoms resolved spontaneously over the ensuing 3 months. Moreover, RNA-sequencing analysis in peripheral blood mononuclear cells revealed that compared with the resolution phase, 106 genes were upregulated in the disease active phase. Most of those differentially expressed genes were related to immune and inflammatory responses, especially NF-κB and its subunits, suggesting that a virus- or bacterium-encoded molecule activates the NF-κB signaling pathway, enhances glucocorticoid signal transduction, and leads to glucocorticoid hypersensitivity syndrome. Although we did not perform transcriptomic analysis of the peripheral blood mononuclear cells in our case, the increases in the ESR and C-reactive protein level in the disease active phase indicate the presence of inflammation. A positive rubella virus IgM antibody prompts that the patient had active rubella during the disease active phase. A positive rubella virus IgG antibody is evidence for a past history of rubella. The etiology of glucocorticoid hypersensitivity syndrome in our case may be associated with the rubella virus infection.

Conclusion

In conclusion, we present a patient with glucocorticoid hypersensitivity syndrome who gradually recovered spontaneously. It is likely that rubella virus infection may be associated with a transient postreceptor defect and enhanced glucocorticoid signal transduction, thereby leading to the corresponding clinical manifestation and compensatory hypoactivation of the HPA axis. To our

knowledge, this is the first report about glucocorticoid hypersensitivity syndrome associated with an underlying rubella virus infection.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Iida S, Nakamura Y, Fujii H, et al. A patient with hypocortisolism and Cushing's syndrome-like manifestations: cortisol hyperreactive syndrome. *J Clin Endocrinol Metab*. 1990;70(3):729–737.
2. Brunner E, Baima J, Vieira TC, Vieira JG, Abucham J. Hereditary corticosteroid-binding globulin deficiency due to a missense mutation (Asp367Asn, CBG Lyon) in a Brazilian kindred. *Clin Endocrinol (Oxf)*. 2003;58(6):756–762.
3. Malchoff CD, Malchoff DM. Glucocorticoid resistance and hypersensitivity. *Endocrinol Metab Clin North Am*. 2005;34(2):315–326.
4. Krysiak R, Okopien B. Glucocorticoid hypersensitivity syndrome–a case report. *West Indian Med J*. 2012;61(8):844–846.
5. Fujii H, Iida S, Gomi M, Tsugawa M, Kitani T, Moriwaki K. Augmented induction by dexamethasone of metallothionein IIa messenger ribonucleic acid in fibroblasts from a patient with cortisol hyperreactive syndrome. *J Clin Endocrinol Metab*. 1993;76(2):445–449.
6. Newfield RS, Kalaitzoglou G, Licholai T, et al. Normocortisolemic Cushing's syndrome initially presenting with increased glucocorticoid receptor numbers. *J Clin Endocrinol Metab*. 2000;85(1):14–21.
7. McMaster A, Ray DW. Drug insight: selective agonists and antagonists of the glucocorticoid receptor. *Nat Clin Pract Endocrinol Metab*. 2008;4(2):91–101.
8. Mullan KR, Atkinson AB, Sheridan B. Cyclical Cushing's syndrome: an update. *Curr Opin Endocrinol Diabetes Obes*. 2007;14(4):317–322.
9. Charmandari E, Kino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (Chrousos syndrome) and hypersensitivity. *Endocr Dev*. 2013;24:67–85.
10. Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. *Pediatr Nephrol*. 2012;27(7):1059–1066.
11. Charmandari E, Ichijo T, Jubiz W, et al. A novel point mutation in the amino terminal domain of the human glucocorticoid receptor (hGR) gene enhancing hGR-mediated gene expression. *J Clin Endocrinol Metab*. 2008;93(12):4963–4968.
12. Nicolaides NC, Charmandari E. Novel insights into the molecular mechanisms underlying generalized glucocorticoid resistance and hypersensitivity syndromes. *Hormones (Athens)*. 2017;16(2):124–138.
13. van Rossum EF, Lamberts SW. Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. *Recent Prog Horm Res*. 2004;59:333–357.
14. Nicolaides NC, Lamprokostopoulou A, Polyzos A, et al. Transient generalized glucocorticoid hypersensitivity. *Eur J Clin Invest*. 2015;45(12):1306–1315.