A patient with glucocorticoid hypersensitivity syndrome

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To the Editor: Primary generalized glucocorticoid hypersensitivity is a rare condition characterized by generalized, partial target-tissue hypersensitivity to glucocorticoids. Therefore, low concentration of glucocorticoids is sufficient to effectively maintain the patient's cell physiological effects and to suppress the hypothalamic-pituitary-adrenal axis. Our study aims to provide some insight into when glucocorticoid hypersensitivity should be considered and how to diagnose it. We also propose a diagnostic flow chart for glucocorticoid hypersensitivity for the first time based on our experience and previous literature review. The study was reviewed and approved by the Institutional Review Board of Huashan Hospital, Fudan University (No. KY2020-049).

A 25-year-old man was hospitalized for weight gain. Physical examination showed central obesity with cervical buffalo hump, a rounded face with acne, abdominal purple striae, and marginally increased blood pressure (131/90 mmHg). Dual-energy X-ray absorptiometry revealed the low bone mass. Oral glucose tolerance test showed impaired glucose tolerance. However, plasma cortisol, adrenocorticotropic hormone (ACTH) levels, and 24 h urinary-free cortisol excretion were within the lower limits of normal, and the overnight 1 mg dexamethasone suppression test showed the decreased cortisol level. Furthermore, pituitary contrast/enhanced magnetic resonance imaging and thin layer adrenal computed tomography (CT) scan ruled out the possibility of pituitary adenoma and adrenal tumors. No apparent abnormality found in positron emission tomography-CT excluded the possibility of neuroendocrine tumors secreting hormones acting the same as cortisol.

We first considered the periodic Cushing syndrome. However, consecutive morning urine-free cortisol/creatinine ratios (a method that had a strong correlation with 24 h urinary cortisol) of the patient for four months was significantly lower than the normal controls [Supplementary Figure 1A, http://links.lww.com/CM9/A920], confirming the state of persistent low cortisol levels but no clinical evidence of glucocorticoid insufficiency. Three months later, the patient voluntarily asked for a second admission because of increased body weight and notable purple striae of 1.5 cm in width. Plasma cortisol levels were extremely low, and plasma ACTH levels were in the borderline low normal range. The 24 h urinary-free cortisol excretion was low on four independent days' samples.

The patient developed Cushing syndrome but had normal or low plasma cortisol levels and no clinical evidence of glucocorticoid insufficiency. It may be explained by taking exogenous glucocorticoid or gluco-corticoid hypersensitivity. However, the patient denied any history of taking glucocorticoids, and the result of the psychological assessment indicated that this patient had no apparent abnormalities in psychological status, excluding the probability of taking glucocorticoids deliberately by himself or Munchausen syndrome. On the other hand, his plasma cortisol levels remained extremely low after 2 weeks of hospitalization without syndrome of adrenal insufficiency; thus it was unlikely to take glucocorticoids provided by others. The liquid chromatography-tandem mass spectrometry assay also showed no evidence of common exogenous glucocorticoid intake.

We further isolated the patient's peripheral blood mononuclear cells (PBMCs) and added hydrocortisone *ex vivo* to specifically assess the patient's responsiveness to glucocorticoids. We selected two specific glucocorticoid-responsive genes, FK506 binding protein 5 *(FKBP5)* and glucocorticoid-induced leucine zipper (*GILZ*),[1] and found the peak responses to hydrocortisone occurred in 100 nmol/L hydrocortisone at 6 h after treatment. This concentration and time were then used for subsequent response studies. The messenger RNA (mRNA) expression

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of specific glucocorticoid-responsive downstream genes *FKBP5* and *GILZ* in the patients was significantly higher than that in the controls, which suggested the presence of glucocorticoid hypersensitivity [Supplementary Figure 1B and 1C, http://links.lww.com/CM9/A920].

Consequently, the patient was diagnosed with glucocorticoid hypersensitivity. We conducted literature searches and combined our own medical practice to propose a standard schematic diagram for diagnosing glucocorticoid hypersensitivity [Supplementary Figure 1D, http://links.lww.com/CM9/A920], which is one of the novelties of this research paper.

To elucidate molecular mechanisms, we performed high-throughput sequencing and real-time polymerase chain reaction (PCR) to detect the reported glucocorticoid receptor (*GR*) gene variants and expression. It has been reported that the polymorphism of N363S, resulting in an asparagine-to-serine change at codon 363 in the GRα gene, was associated with increased sensitivity to glucocorticoids. Variants of GRβ (A3669G and G3134T) and *Bcl1* intron mutations also contributed to hypersensitivity likely by eliminating the dominant-negative effects of GRβ. We used whole-exome sequencing to determine GR variants and found no mutations in the *N363S* gene for *GRα* and *GR*β. *Bcl1* single-nucleotide polymorphism (homozygous) in the *GR* gene *(NR3C1,* rs41423247) was detected, which is an intronic mutation and is reported to be associated with hypersensitivity.[2] But the frequency of hetero/homozygote variants of *Bcl1* is estimated to be 35% to 46%, respectively, in the European population,[3] suggesting *Bcl1* polymorphisms may be indirectly related to glucocorticoid hypersensitivity. To evaluate whether the expression of the *GR* contributed to the hypersensitivity, we performed real-time PCR to detect NR3C1, *GRα*, and *GR*β distribution in PBMCs. As shown in Supplementary Figure 1E, http://links.lww.com/CM9/A920 the NR3C1 mRNA expression of the patient was significantly lower than his parents and the normal control, whereas the *GRα* and *GR*β expression did not differ strongly.

Glucocorticoid's hypersensitivity is characterized by being hypersensitive to ultra-low-dose dexamethasone, low plasma cortisol levels, and Cushing syndrome manifestation such as low bone mineral density and metabolism syndrome without clinical evidence of adrenal insufficiency. Patients with such clinical manifestations should be differentiated to periodic Cushing syndrome or exogenous glucocorticoid intake. In the present case, the sequential morning urine-free cortisol-to-creatinine ratios of patient continued to be low, and therefore the diagnosis of Cushing syndrome is not likely. However, it may be challenging to exclude the possibility of exogenous glucocorticoid intake in clinical practice. Although we obtained the medical history of exogenous glucocorticoid administration, reliability and accuracy will be compromised for the following two reasons. First, a very small number of patients deliberately conceal their medical history and repeatedly seek medical care, which is called Munchausen syndrome and is often accompanied by cognitive and psychological disorders. But our patient only had mild-to-moderate severity of anxiety after the psychological evaluation. Second, the patient took the drug without realizing it. The patient was admitted twice and was bought out from the possible dosing environment; the plasma cortisol level continued to be low after 2 weeks of hospitalization without clinical attack of adrenal insufficiency, which was an important clue for the consideration of glucocorticoid hypersensitivity. After exploring any possible event that may cause hypercortisolism, we speculated that the patient's cells overreacting to glucocorticoids may explain. Mass spectrometry further excluded the possibility ofexogenous glucocorticoid intake. Based on this, glucocorticoid hypersensitivity was speculated and was confirmed by molecular function test *ex vivo*.

We also performed high-throughput sequencing and real-time PCR to detect the *GR* gene variants and expression to elucidate molecular mechanisms. There was a homozygous Bcl1 mutant in our patient, an intron mutation which reported to associate with glucocorticoid hypersensitivity. It is notable that *GR* polymorphisms affect glucocorticoid sensitivity in a tissue-specific manner by altering *GR* function or possibly because of linkage to a locus that controls hormone access to the receptor by influencing steroid metabolism. The mRNA results showed a decreased expression of *GR* receptor in the patient. We speculated that decreased *GR* expression in our patient was secondary to enhanced glucocorticoid sensitivity and was supported by another study that dexamethasone decreased *GR* mRNA levels to approximately 50% of control.[4] Owing to the limited collection of specimens, we look forward to having an in-depth exploration after constructing induced pluripotent stem cells.

In terms of the treatment of glucocorticoid hypersensitivity, the therapeutic effect of ketoconazole and cabergoline was not satisfactory. *GR* antagonists, especially mifepristone, seem to be the optimum for impeding GR activity and relieving Cushingoid symptoms. Liu *et al*[5] reported a case that the mifepristone was administered to the patient with satisfactory effects in terms of improved electrolyte level, lipid metabolism, and bone metabolism. Our patient was treated with hypotensor drugs and metformin. Mifepris-tone was suggested but the patient refused. The patient's condition was stable in the follow-up visits.

In summary, patients with Cushing syndrome and normal or low plasma cortisol levels without clinical evidence of glucocorticoid insufficiency were considered to have specific conditions of periodic Cushing syndrome, exogenous glucocorticoid intake, or glucocorticoids hypersensitive. Our reported case provides some insight into when to suspect glucocorticoid hypersensitivity and summarizes the standardized procedures for diagnosing glucocorticoid hypersensitivity. Isolation of the patient's cells to test the response to glucocorticoid would provide direct evidence of hypersensitivity, and genetic testing may then be required.

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Conflicts of interest

None.

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