Two cases of infantile-onset primary generalized glucocorticoid hypersensitivity and the effect of mifepristone

Xiu Zhao1, Zhongwei Xu1, Huiping Su1, Rongfei Zheng1, Min Zhan2, Yuge Huang3 and Zhe Su1*

Abstract
Background: Primary generalized glucocorticoid hypersensitivity (PGGH) is a very rare disease caused by terminal organ hypersensitivity to glucocorticoids for which the aetiology is unknown. The incidence of PGGH is extremely rare, especially in children. To date, the literatures about the etiology, prognosis and treatment of PGGH are scarce. Aim of the study is describing the cases of two Chinese children with infantile-onset PGGH in one family, one of whom died and one who was treated with mifepristone. They are the two youngest children with PGGH reported in the literature.

Case presentation: Two siblings with infantile-onset PGGH were affected in this family. The main manifestations of patient 1 were typical Cushing’s syndrome-like manifestations, significantly aggravated symptoms after physiological doses of glucocorticoids and very low levels of serum cortisol and adrenocorticotropin hormone (ACTH) during attacks. After being diagnosed with PGGH, he was given guidance to avoid glucocorticoids and took mifepristone therapy for 5 months, and his symptoms improved. Patient 2 was the younger brother of patient 1, with similar manifestations to his brother at the age of 4 months. Patient 2 ultimately died at the age of 9 months.

Conclusion: PGGH is a very rare disease that can lead to death if not diagnosed and treated in a timely manner. This article describes the cases of the two youngest children with PGGH reported in the literature, one of whom improved after mifepristone treatment, and increases the knowledge of the clinical manifestations of and the treatment experience in PGGH.

Keywords: Primary generalized glucocorticoid hypersensitivity, Cushing syndrome, Glucocorticoids, Mifepristone

Background
Primary generalized glucocorticoid hypersensitivity (PGGH) is a disease caused by terminal organ hypersensitivity to glucocorticoids for which the aetiology is unknown [1]. PGGH is characterized by an overreaction of target organs to corticosteroids, which is characterized by the presence of Cushing’s syndrome-like manifestations and normal/low blood cortisol and adrenocorticotropin hormone (ACTH) levels [2]. The incidence of PGGH is extremely rare. To date, only 16 cases have been reported, of which only 4 were children [3–6]. At the same time, there are few reports on the treatment and prognosis of PGGH. This paper reports the cases of two children with infantile-onset PGGH in one Chinese family, one of whom was treated with mifepristone.

Case presentation
Patient 1 (see Figs. 1 and 2 and Table 1), the proband, was a 3-year and 7-month-old boy. He was admitted because of growth retardation for 3 years and rapid weight gain for...
Fig. 1 The growth pattern of patient 1 before and during mifepristone treatment. HC: hydrocortisone. A Weight-for-height curves (WHO). B Height-for-age curves (WHO)
more than 2 years. Since the age of 8 months, he has been stunted, with a low height standard deviation (SD) score from $-1.25$ SD to $-2.04$ SD. His weight increased rapidly after the age of 2 years. During the age of 2–3 years, his weight gain varied regularly, with 1–2 weeks of rapid gain followed by 2–4 weeks of slower gain. After the age of 3 years, his weight increased continuously, from $-0.24$ SD to $+4.89$ SD (weight-to-height standard score), and he had hirsutism, a moon face and acne, fatigue, reduced physical capacity and decreased cognitive ability. In an external hospital, he was diagnosed with adrenal insufficiency because of the significantly decreased serum cortisol and ACTH and given hydrocortisone (HC) 7.5 mg (9.38 mg/m²/d). During the 2-month HC treatment, the above symptoms were further aggravated.

As the first child of nonconsanguineous parents, he was born at 38 + 5 weeks of gestation via vaginal delivery, and his birth weight was 3.3 kg. He had suffered from oral Candida infections and pneumonia. No abnormalities in the history of birth, feeding, psychomotor development, operations or vaccinations were reported. The patient had two younger brothers. The elder younger brother is patient 2. The other brother died of an intracranial haemorrhage at the age of 1 week without manifestations similar to his siblings. His mother had a spontaneous miscarriage at the first trimester of her second pregnancy (see Fig. 3).

Physical examination: Height, 92.4 cm ($-2.04$ SD); weight, 20 kg (weight-to-height standard score $+4.89$ SD); body mass index (BMI), 23.43 kg/m² ($> 97$th percentile (P97th) $=17.6$); and blood pressure (BP), 90–133/49–87 mmHg (83.3% systolic blood pressure (SBP) $> P95$th, 56.3% diastolic blood pressure (DBP) $> P95$th). He was expressionless. He showed symptoms of Cushing’s syndrome, such as central obesity, a moon face and flushed, ruddy face, acne, a buffalo hump, and hirsutism (Ferriman-Gallwey score: 12) without striae or axillary hair. He had bilateral knee valgus with 5 cm of ankle spacing. He had normal male external genitalia, with Tanner stage 1. There were no abnormalities of the heart, lung, abdomen, muscle strength, or muscle tension.

Laboratory examination: The results of complete blood count, routine urine, routine faecal, liver and kidney function, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), neuron-specific enolase (NSE), human chorionic gonadotropin (HCG), atrial natriuretic peptide and thyroid function analyses were normal. High-density lipoprotein cholesterol was 0.94 mmol/L. The levels of IGF-1 and IGFBP3 were 291 ng/ml ($78.2 \pm 31.2$ ng/ml) and 3.9 μg/ml ($1.99 \pm 0.5$ μg/ml), respectively. The glucose tolerance test result was normal. Before the usage of HC, 8 AM cortisol and ACTH were 2.0–4.28 μg/dl (reference range 5–23 μg/dl) and 9.04–19.78 pg/ml (10–80 pg/ml), respectively. The levels of androstenedione (AD), dehydroepiandrosterone (DHEAS), testosterone (T), progesterone (P) and 17-hydroxyprogesterone (17-OH-P) were lower than normal. The levels of renin activity, angiotensin II and aldosterone were normal. After the withdrawal of HC, the levels of serum 8 AM cortisol and ACTH and 24-hour urinary free cortisol were normal.
(UFC) were undetectable. His parents’ serum 8 AM ACTH and cortisol levels were normal. No abnormalities were found on electrocardiography (ECG) or ultrasonography of the heart, liver, gallbladder, pancreas, spleen, urinary system, adrenal gland, retroperitoneum, abdominal aorta, renal artery, or carotid artery. No abnormality was found in the magnetic resonance imaging (MRI) of the brain and pituitary. The whole-genome sequencing found no pathogenic or possibly pathogenic mutations and no copy number variations or chromosome abnormalities related to the clinical manifestations of the patient. No pathogenic gene mutations related to the phenotype were found in the patient’s mitochondrial genome.

Diagnosis, Treatment and follow-up: The patient stopped taking HC immediately and avoided contact with any form of glucocorticoid. He was given diet and exercise management and antihypertension treatments. After the 1-month follow-up, the patient’s weight still increased rapidly, and his hypertension, hirsutism, acne and fatigue did not improve. The 8 AM cortisol and ACTH and 24-hour UFC levels were still lower than normal. He was diagnosed as PGGH according to excessive glucocorticoid manifestations and the low serum
cortisol and ACTH. After discussion with pharmaceutical experts, oral treatment with mifepristone 25 mg once a day (1.2 mg/kg/d) was started. After 2.5 months of mifepristone treatment, the patient's height increased 2.2 cm, and his activity, exercise capacity, acne and hirsutism significantly improved, but no obvious change in BP was observed. Due to continued weight gain and physical capacity problems, mifepristone was given orally at a dosage of 25 mg twice a day. After 5 months of mifepristone treatment, his weight and BMI began to decrease, accompanied by good growth (5.7 cm/5 months). His acne disappeared, and his hirsutism improved. He was full of energy, similar to a healthy boy. His parents were satisfied with the current treatment effect.

Patient 2 (see Figs. 4 and 5) was a younger brother of the proband. He was born at 38 weeks of gestation via vaginal delivery, and his birth weight was 3.3 kg. At the age of 8 days, he was admitted because of necrotizing enterocolitis and sepsis, for which he was treated with methylprednisolone for 2 days. At 1.6 months after birth, exploratory laparotomy and partial ileectomy were performed because of ileal perforation. Intestinal obstruction with malnutrition was relieved by conservative treatment. At the age of 4 months, a small amount of mometasone ointment was used because of rash. After that, he experienced rapid weight gain and slowed growth. His weight increased 5.44 kg over the next 4 months without extra food intake. At the ages of
5.3 months and 6.6 months, respectively, he was admitted because of severe obesity. At the age of 6.6 months, hypertension (BP 100–110/68 mmHg) and low cortisol (0.42 μg/dl) were found. Mometasone ointment was discontinued, and HC (11.3 mg/m²/d) was given orally in consideration of secondary adrenocortical insufficiency. At the age of 8 months, he was admitted to the PICU because of anhelation and severe obesity. Physical examination: Temperature, 36.7 °C; pulse, 172 beats/min; respiratory rate, 70 times/min; BP, 143/91 mmHg; weight, 9.5 kg (weight-to-height standard score +3.23 SD); length, 64 cm (−3.04 SD); head circumference, 42.5 cm; oxygen saturation (sPO2), 88%; obese; a full-moon and flushed, ruddy face; and a buffalo hump. The breathing sounds of both lungs were coarse, and no rales were heard. The heart rate was 172 beats per minute, but no gallop rhythm or murmur were heard. An old surgical scar could be seen in the middle of the abdomen, but no other abnormalities were found in the physical examination. Laboratory examination: The level of 8 AM cortisol (0.42–1.46 μg/dl), ACTH (<5.05 pg/ml), DHEAS, AD and T were lower than the normal values. Liver and kidney function, electrolytes, glucose, CEA, AFP, HCG, NSE and ECG findings were normal. The results of ultrasonography of the heart, liver, gallbladder, pancreas, spleen, urinary system, and both adrenal glands were normal. No abnormality was found by abdominal computed tomography (CT). Unfortunately, the boy died at the age of 9 months with the corresponding treatments including dexamethasone and HC. At last he also was diagnosed as PGGH according to Cushing’s syndrome-like manifestations and the low serum cortisol and ACTH.

Discussion and conclusions

PGGH is a very rare and lethal disease for which there is limited experience in treatment. This article describes the cases of 2 children with infantile-onset PGGH in a Chinese family. The two siblings are the youngest patients with PGGH reported thus far. Patient 2 died, and patient 1 improved with mifepristone treatment.

Here, we presented the cases of two boys with infantile-onset excessive glucocorticoid manifestations [3], including central obesity, Cushing’s syndrome-like symptoms, and growth retardation with significant weight gain. As a history of contact with alcohol or viral infections was excluded, the low serum cortisol and ACTH may have been due to periodic Cushing’s syndrome or PGGH. Because there was no increase in cortisol even during the clinical exacerbation period, periodic Cushing’s syndrome could be excluded. Therefore, on the basis of the aggravation of symptoms after the use of low-dose or...
even physiological doses of glucocorticoids in the past, the diagnosis of PGGH was confirmed.

The spectrum of sensitivity to glucocorticoids in the population is continuous [7]. During glucocorticoid therapy in patients with congenital adrenocortical hyperplasia, nephrotic syndrome or rheumatoid arthritis, sensitivity to glucocorticoids shows some individual differences [8]. The extremes of the spectrum are glucocorticoid hypersensitivity and glucocorticoid insensitivity syndrome (GIS). There are many factors affecting glucocorticoid sensitivity, including genomic effects and nongenomic effects. These factors include changes in the bioavailability of glucocorticoids, the concentration of corticosteroid binding globulin, the balance of 11βHSD1 and 11βHSD2 activity, multidrug resistance (MDR) pump activity and its gene polymorphisms, an increase in glucocorticoid receptor (GR) α, the enhanced binding ability of GRs to glucocorticoids, the activation of NF-κB in the post-GR receptor pathway, abnormal cytokines/molecular chaperones regulating GR action, and GR gene mutations/polymorphisms [8, 9]. Abnormalities related to GR are the most likely pathogenesis of PGGH. Glucocorticoids act mainly through GR, which is encoded by the NR3C1 gene. After variable splicing of exon 9, this gene forms GRα and GRβ. GRα is widely expressed and binds to glucocorticoids, while GRβ does not bind to glucocorticoids but has a negative effect on GRα [10]. Laboratory studies have found that GRβ can form a dimer with GRα and directly regulate the expression of downstream genes [11–13].

It is difficult to identify the aetiology of PGGH, which can be found in only a few case studies. To date, studies in patients have found that possible causes include infection (such as rubella infection) [1], abnormal thermal stability and hGR affinity [14], an increase in hGR with normal affinity [3], an abnormal NF-κB response in the GR post-receptor signal transduction pathway [4] and abnormal gene levels. The possible mechanisms that cause PGGH at the genetic level include the increased GR sensitivity due to the NR3C1 gene polymorphisms p.N363S and Bc1; the p.D401H mutation in the NR3C1 gene, which can lead to tissue-selective glucocorticoid hypersensitivity; and the p.G3134T mutation in the NR3C1 gene, which can lead to systemic glucocorticoid hypersensitivity [15–20]. While no mutation was found in either patient in this report. Further studies on GR should be considered.

There are few reports on the prognosis of PGGH (see Table 2). Three untreated patients with PGGH were in spontaneous remission [1, 4], but there were also deaths, as seen in patient 2. Despite guidance to follow a strict diet and proper exercise to control weight and to avoid any contact with glucocorticoids, the symptoms and laboratory parameters of patient 1 were still aggravated. Given that his PGGH symptoms were not temporary and the death of his younger brother, patient 1 needed to be treated as soon as possible.

To date, only 3 patients with PGGH were treated with drugs (see Table 2). Because of the low level of cortisol in blood, mifepristone was the first choice to act on GR. Mifepristone has been approved by the Food and Drug Administration (FDA) and several international guidelines for the treatment of Cushing’s syndrome [9, 24, 25]. Mifepristone has a similar structure to progesterone and glucocorticoids and works by selectively antagonizing progesterone receptors at low doses and antagonizing GR at high doses. Mifepristone can act on GRα and GRβ and directly regulate GRβ gene expression independent of GRα [26]. The affinity of mifepristone is 18 times that of cortisol, and mifepristone can effectively improve the clinical syndrome caused by hypercortisolism. In addition to an adult female patient with PGGH who used ketoconazole because mifepristone was not available [21], a 27-year-old male patient and a 13.75-year-old girl with PGGH were treated with mifepristone, and their symptoms were improved [5, 22]. The experience with mifepristone in children is very limited. Patient 1 is the youngest patient with PGGH reported to be treated with mifepristone. Due to the experience of mifepristone treatment in the adult patients with PGGH and Cushing’s syndrome, the dosage of mifepristone in PGGH should be lower than that administered for Cushing’s syndrome. Therefore, the initial dose administered for patient 1 was 1.2 mg/kg/d (25 mg qd). The dose was gradually increased according to the situation during the follow-up, and the adverse reactions of mifepristone were monitored [20]. Within 5 months of treatment, his clinical manifestations were relieved. His height developed well, and his weight decreased. His physical capacity and activity returned to normal. The only adverse reaction during treatment was mild hypokalaemia.

Our report provides the more information of clinical manifestations, treatment and prognosis for paediatric patients with PGGH. While the aetiology of PGGH in these two cases still could not be found. The more study of aetiology will be our future research continually.

PGGH is a very rare disease. When a child with obvious cushingoid features in presence of reduced ACTH and cortisol levels without exogenous hormone exposure, PGGH should be diagnosis. It is dangerous to treat the patient with PGGH with hydrocortison or other glucocorticoids. PGGH can be lethal without timely diagnosis and correct treatment. This article described the cases of the two youngest children with PGGH reported in the literature, one of whom was the youngest patient treated with mifepristone, and
| Author          | case | Age (year) | Gender | Ethnicity | Family history | GC exposure | Clinical manifestation | Cortisol (nmol/L) | ACTH (pmol/L) | 24hUFC (nmol/24 h) | Imaging of adrenal gland | Treatment | Prognosis       |
|-----------------|------|------------|--------|-----------|----------------|-------------|------------------------|-------------------|--------------|-------------------|--------------------------|-----------|----------------|
| Our case        | 1    | 3.6        | M      | Chinese   | +              | +           | central obesity, hirsutism, moon face, acne, buffalo hump, fatigue, decreased cognitive ability, hypertension | 0.00–117.27       | 0.00–435     | undetectably low | normal                   | mifepristone | remission       |
|                 | 2    | 0.55       | M      | Chinese   | +              | +           | central obesity, moon face, acne, buffalo hump, hypertension | 11.51–40          | <1.00        | normal            | no                       | death      |                |
| Russcher et al. | 3    | 13         | F      | Netherlander | –              | +           | obesity, fatigue, growth retardation, violaceous striae, osteopenia | <30               | <3.00        | normal            | stop using budesonide   | spontaneous | remission       |
| Newfield et al. | 4    | 10.8       | F      | American  | –              | –           | central obesity, moon face, buffalo hump, violaceous striae, osteopenia, learning disability, early puberty | 304.18 ± 15.28    | 6.09 ± 2.35 | normal            | normal                   | mifepristone | remission       |
| Nicolaides et al. | 5    | 9          | F      | Greek     | –              | –           | central obesity, moon face, buffalo hump, violaceous striae, acanthosis nigricans, hirsutism | 0.45–7.79          | 1.00         | 900               | normal                   | no                    | spontaneous remission       |
| Su, et al.      | 6    | child      | NM     | Chinese   | –              | –           | central obesity, moon face, buffalo hump, violaceous striae, hirsutism, hypertension, growth retardation, ostalgia | Low               | Normal      | Low               | normal                   | NM                     | NM                |
| Author          | case | Age (year) | Gender | Ethnicity | Family history | GC exposure | Clinical manifestation                                      | Cortisol (nmol/L) | ACTH (pmol/L) | 24hUFC (nmol/24 h) | Imaging of adrenal gland | Treatment | Prognosis     |
|-----------------|------|------------|--------|-----------|----------------|-------------|-----------------------------------------------------------|------------------|--------------|-------------------|--------------------------|------------|---------------|
| Iida et al.     | 7    | 54         | M      | Japanese  | +              | –           | central obesity, moon face, buffalo hump, DM              | 2000 ± 19.00     | <2.00        | 4000–5000         | normal                   | NM         | NM            |
| Krysiak et al.  | 8    | 28         | F      | Polish    | –              | –           | Obesity, hypertension, prediabetes, osteopenia            | 1203.1           | <2.00        | 272.4–317.8      | adrenal gland atrophy      | ketoconazole, cabergoline  | death         |                |
| Liu et al.      | 9    | 27         | M      | Chinese   | +              | –           | central obesity, moon face, buffalo hump, violaceous striae, osteopenia | 1075             | <0.22        | 11.95             | adrenal gland atrophy      | mifepristone             | remission     |
|                 | 10   | adult      | M      | Chinese   | +              | –           | hypertension, moon face, buffalo hump, violaceous striae, osteopenia, hyperglycemia | NM               | <0.22        | 23.62             | normal                   | no                     | exacerbation  |
| Al-Shoumer et al. | 11  | 32         | F      | Kuwaitis  | –              | +           | obesity, moon face, buffalo hump, violaceous striae, DM, renal calculus, myasthenia, hypertension | 28               | <1.00        | undetectably low concentration | adrenal myelolipoma      | NM         | NM            |
| Zhang et al.    | 12   | 29         | M      | Chinese   | –              | –           | central obesity, moon face, buffalo hump, violaceous striae, acne, osteopenia, hypokalemia, impaired glucose tolerance, hypertension | 7264–2165.6      | 560–956      | 378.12            | normal                   | no                     | spontaneous remission    |
| Author case | Age (year) | Gender | Ethnicity | Family history | GC exposure | Clinical manifestation | Cortisol (nmol/L) | ACTH (pmol/L) | 24hUFC (nmol/24h) | Imaging of adrenal gland | Treatment | Prognosis |
|-------------|------------|--------|-----------|----------------|-------------|-----------------------|------------------|-------------|------------------|-------------------------|-----------|-----------|
| Santen, et al. [17] | 13 | F | American | + | + | obesity, moon face, fatigue, headache, abdominal pain, nausea, diarrhea, anxiety/depression, muscle and joint aches, hypertension | 6300–9800 | 276.00 | NM | no | GC | NM | NM |
increases the knowledge of the clinical manifestations of and the treatment experience in PGGH.

Abbreviations
ACTH: Adrenocorticotropic hormone; AD: Androstenedione; AFP: Alpha-fetoprotein; BP: Blood pressure; CEA: Carcinoembryonic antigen; DBP: Diastolic blood pressure; DHEAS: Dehydroepiandrosterone; ECG: Electrocardiography; FDA: Food and Drug Administration; GIS: Glucocorticoid insensitivity syndrome; GR: Glucocorticoid receptor; HC: Hydrocortisone; HCG: Human chorionic gonadotropin; MDR: Multidrug resistance; MR/MRI: Magnetic resonance imaging; NSE: Neuron-specific enolase; P: Progesterone; PGGH: Primary generalized glucocorticoid hypersensitivity; SD: Standard deviation; SBP: Systolic blood pressure; sPO2: Oxygen saturation; T: Testosterone; UFC: Urinary free cortisol; 17-OH-P: 17-hydroxypregesterone.

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Authors' contributions
XZ contributed to the data collection, data interpretation and writing of the manuscript. ZS contributed to the study design and reviewed the report. RFZ contributed to the revision of the manuscript. YGH, MZ contributed to the clinical data collection and data interpretation. ZWX contributed to the imaging data collection and data interpretation. HPS contributed to the gene variant interpretation. All authors have read and approved the manuscript.

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Availability of data and materials
The dataset analyzed in the current study is available from the corresponding author upon reasonable request.

Declarations
Ethics approval and consent to participate
This study was approved by the ethics committee of Shenzhen Children’s Hospital (No. 2022 [002]). All of the subjects provided written informed consent in accordance with the Declaration of Helsinki.

Consent for publication
Written parental consent for publication was obtained on behalf of each of the children. Written consent for publication was obtained from all of the adults whose information is provided in this case report.

Competing interests
We declare that we have no financial and personal relationships with other people or organizations that could inappropriately influence our work, and there are no professional or other personal interests of any nature or type in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Author details
1Department of Endocrinology, Shenzhen Children’s Hospital, 7019# Yitian Road, Futian District, Shenzhen 518038, Guangdong Province, China. 2Pharmacy Department, Shenzhen Children’s Hospital, Shenzhen 518000, Guangdong Province, China. 3Department of Pediatrics, the Affiliated Hospital of Guangdong Medical University, Zhanjiang 524023, Guangdong, China.

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References
1. Zhang Z, Feng Y, Cao Y, Chen Y, Li F. A Case of Glucocorticoid Hypersensitivity Syndrome Associated With Underlying Rubella Virus Infection. AACE Clin Case Rep. 2021;7:367–71.
2. Charmandari E. Primary generalized glucocorticoid resistance and hypersensitivity. Horm Res Paediatr. 2011;76:145–55.
3. Huizenga NA, Koper JW, de Lange P, Pols HA, Stolk RP, Grobbée DE, et al. Interperson variability but intraperson stability of baseline plasma cortisol concentrations, and its relation to feedback sensitivity of the hypothalamo-pituitary-adrenal axis to a low dose of dexamethasone in elderly individuals. J Clin Endocrinol Metab. 1998;83:47–54.
4. Quax RA, Manenschijn L, Koper JW, Hazes JM, Lamberts SW, van Rossum EF, et al. Glucocorticoid sensitivity in health and disease. Nat Rev Endocrinol. 2013;9:670–86.
5. Nicolaides NC, Charmandari E. Novel insights into the molecular mechanisms underlying generalized glucocorticoid resistance and hypersensitivity syndromes. Hormones (Athens, Greece). 2017;16:124–38.
6. Su C, Yuchuan L, Chunxiu G. A Case of Glucocorticoid Hypersensitivity Syndrome. In: Endocrine and Metabolic Diseases Symposium and Young and Middle-aged English Forum, vol. 2, 2008.
7. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol. 2013;132:1033–44.
8. Oakley RH, Jeffell CM, Yudt MR, Boftetaido DM, Cidlowski JA. The dominant negative activity of the human glucocorticoid receptor beta isoform. Specificity and mechanisms of action. J Biol Chem. 1999;274:27857–66.
9. Lewis-Tuffin LJ, Jeffell CM, Bierstock RJ, Collins JB, Cidlowski JA. Human glucocorticoid receptor beta binds RU-486 and is transcriptionally active. Mol Cell Biol. 2007;27:2266–82.
10. He B, Cruz-Topete D, Oakley RH, Xiao X, Cidlowski JA. Human Glucocorticoid Receptor beta Regulates Glucconeogenesis and Inflammation in Mouse Liver. Mol Cell Biol. 2015;35:714–30.
11. Iida S, Nakamura Y, Fujii H, Nishimura J, Tsugawa M, Gomi M, et al. A patient with hypopituitarism and Cushings syndrome-like manifestations: cortisol hyperreactive syndrome. J Clin Endocrinol Metab. 1990;70:729.
12. Russcher H, Smit P, van Rossum EF, van den Akker EL, Brinkmann AO, de Heide LJ, et al. Strategies for the characterization of disorders in cortisol sensitivity. J Clin Endocrinol Metab. 2006;91:694–701.
13. Nicolaides NC, Lamprokostopoulos A, Polyzos A, Kino T, Katsantonis E, Triantafyllou P, et al. Transient generalized glucocorticoid hypersensitivity. Eur J Clin Investig. 2015;45:1306–15.
14. Charmandari E, Ichio T, Jubiz W, Baid S, Zachman K, Chrousos GR, 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;93:4963–8.
15. Charmandari E, Kino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (Chrousos syndrome) and hypersensitivity. Endocr Dev. 2013;24:67–85.
16. Santen RJ, Jeffell CM, Yue W, Heijtjan DF, Raff H, Katen KS, et al. Glucocorticoid Receptor Mutations and Hypersensitivity to Endogenous and Exogenous Glucocorticoids. J Clin Endocrinol Metab. 2018;103:3630–9.
17. Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, et al. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab. 1998;83:144–51.
18. Charmandari E. Primary generalized glucocorticoid resistance and hypersensitivity: the end-organ involvement in the stress response. Sci Signal. 2012;5:t5.
19. Koetz NR, van Rossum EF, Vents M, Dieidelich S, Quinkler M, Bcll polymorphism of the glucocorticoid receptor gene is associated with increased bone resorption in patients on glucocorticoid replacement therapy. Clin Endocrinol. 2013;78:831–7.
20. Brown DR, East HE, Eilerman BS, Gordon MB, King EE, Knecht LA, et al. Clinical management of patients with Cushing syndrome treated with mifepristone: consensus recommendations. Clin Diabetes Endocrinol. 2020;6:1–18.
21. Liu Y, Han M, Yang J, Xu Q, Xu L, Ren Y, et al. Primary Generalized Glucocorticoid Hypersensitivity Treated with Mifepristone: A Case Report. Int J Gen Med. 2020;13:825–31.
22. Newfield RS, Kalaitzoglou G, Licholai T, Chilton D, Ashraf J, Thompson EB, et al. Normocortisolemic Cushing’s syndrome initially presenting with increased glucocorticoid receptor numbers. J Clin Endocrinol Metab. 2000;85:14–21.
23. Al-Shoumer KA, Hafez MF, Dodi SA. A case of hypocortisolemic clinical Cushing’s syndrome. Ann Saudi Med. 2008;28:124–7.
24. Ceccato F, Boscaro M. Cushing’s Syndrome: Screening and Diagnosis. High Blood Press Cardiovasc Prev. 2016;23:209–15.
25. Group CPAC. Consensus of Chinese Experts on diagnosis and treatment of Cushing’s Disease (2015). Natl Med J China. 2016;96:835–40.
26. Krysiak R, Okopien B. Glucocorticoid hypersensitivity syndrome—a case report. West Indian Med J. 2012;61:844–6.

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