BMC Pediatrics

CASE REPORT

Open Access

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

Xiu Zhao[1], Zhongwei Xu[1], Huiping Su[1], Rongfei Zheng[1], Min Zhan[2], Yuge Huang[3] and Zhe Su[1*]

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

*Correspondence: su_zhe@126.com

[1] Department of Endocrinology, Shenzhen Children's Hospital, 7019# Yitian Road, Futian District, Shenzhen 518038, Guangdong Province, China
Full list of author information is available at the end of the article

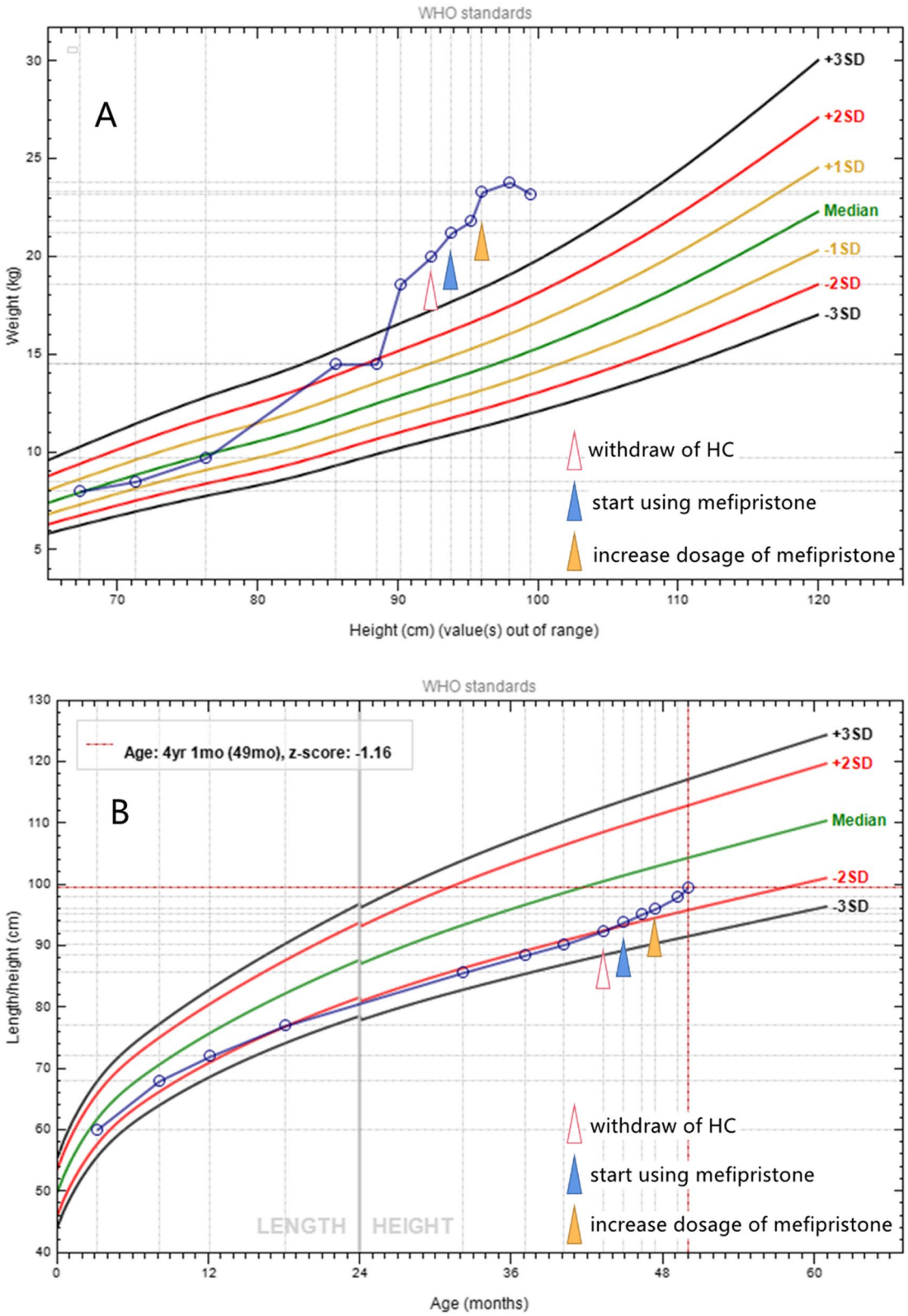

Fig. 1 The growth pattern of patient 1 before and during mifepristone treatment. HC: hydrocortisone. **A** Weight-for-height curves (WHO). **B** Height-for-age curves (WHO)

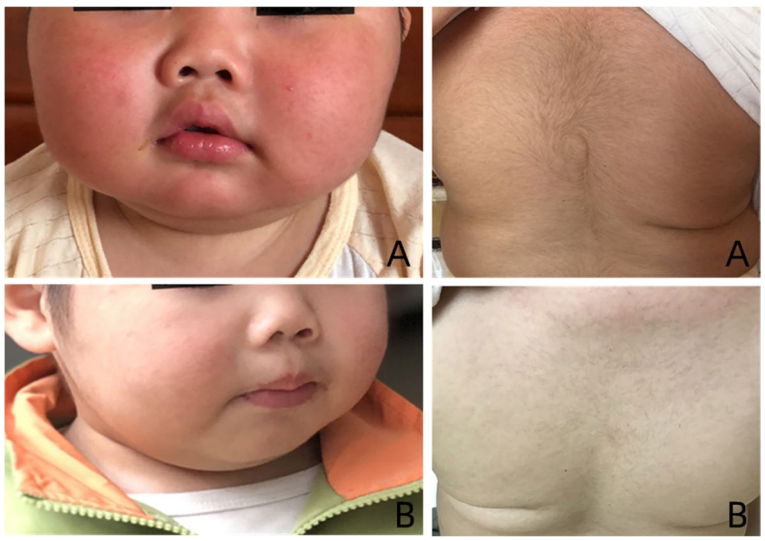

Fig. 2 The change in Cushing's syndrome-like manifestations in patient 1 before and during treatment with mifepristone. **A** Before the treatment; **B** After 5 months of treatment

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/m^2/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/m^2 (> 97th percentile (P97th) =17.6); and blood pressure (BP), 90–133/49–87 mmHg (83.3% systolic blood pressure (SBP) > P95th, 56.3% diastolic blood pressure (DBP) > P95th). He was expressionless. He showed symptoms of Cushing's syndrome, such as central obesity, a full moon 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 ± 31.2 ng/ml) and 3.9 μg/ml (1.99 ± 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

Table 1 The data of patient 1 before and during mifepristone treatment

Age	3 yr and 4 mo	3 yr and 6 mo		3 yr and 8 mo	3 yr and 10 mo	3 yr and 11 mo	4 yr and 1 mo	4 yr and 2 mo
treatment	before HC treatment	1-mo HC treatment		HC treatment stopped for 1 mo, mifepristone treatment started	mifepristone (25 mg qd) x 1.5 mo	mifepristone (25 mg qd) x 2.5mo	mifepristone (25 mg bid) x 2 mo	mifepristone (25 mg bid) x 2.5 mo
Ht (cm)	90.2	92.4		93.8	95.2	96.0	98.0	99.5
Wt (kg)	18.6	20.0		21.2	21.8	23.2	23.8	23.2
BMI (kg/m^2)	22.9	23.4		24.1	24.1	25.2	24.8	23.4
BP (mmHg)	/	90-133/49-87		89-123/50-81	93-118/54-82	90-128/50-76	93-123/51-86	120-130/75-85
Ferriman-Gallwey score	/	12		12	8	8	6	6
Active communication	seldom	seldom		seldom	more	more	normal	normal
Physical capacity	walk a few tens of metres	walk a few tens of metres		walk a few tens of metres	walk 200-300 metres	walk 500-800 metres	normal	normal
Expression	apathy	apathy		apathy	mobile	mobile	mobile	mobile
8AM CORT (μg/dl)	2.0-4.28	0.0-0.2		0.0-0.3	/	/	0.2	< 0.5-0.7
8AM ACTH (pg/ml)	9.04-19.78	5.88-6.06		4.4-8.36	/	/	2.98	< 1.5-2
24hUFC (μg)	/	0.0		0.0	/	/	0.9	/
Adrenal intermediate metabolites (DHEAS, AD, P, 17-OH-P, T)	low	low		low		low	low	

HC Hydrocortisone, *Ht* Height, *Wt* Weight, *BP* Blood pressure, *BMI* Body mass index, *ACTH* Adrenocorticotropin hormone, 24hUFC: 24-hour urine free cortisol, *yr* year, *mo* month, *AD* Androstenedione, *DHEAS* Dehydroepiandrosterone, *T* Testosterone, *P* Progesterone, *17-OH-P* 17-hydroxyprogesterone. The blue part indicates the data before hydrocortisone treatment. The red part indicates the data during hydrocortisone treatment. The white part indicates the data after stopping hydrocortisone treatment. The yellow part indicates the data during the mifepristone treatment. The light and dark yellow parts indicate different dosages of mifepristone (25 mg qd and 25 mg bid) treatment

(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

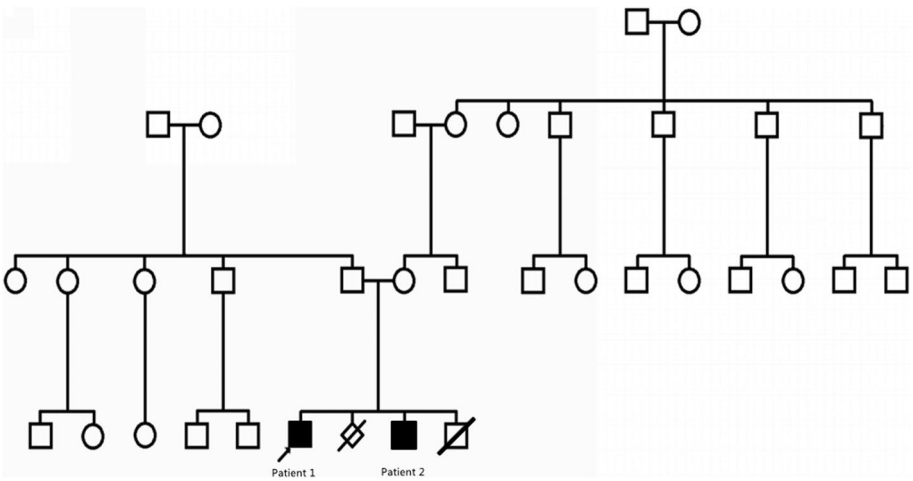

Fig. 3 The pedigree of patient 1 and patient 2

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

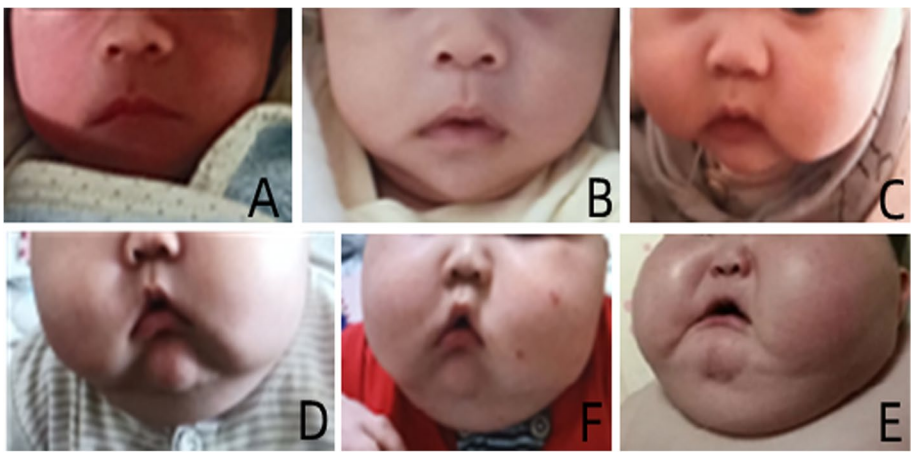

Fig. 4 The data of patient 2 from the age of 8 days to 9 months. **A** 8 days old. **B** 2 months old. **C** 4 months old before treatment with mometasone ointment. **D** 5 months old during the treatment with mometasone ointment. **E** 6.6 months old without treatment with mometasone ointment. **F** 8 months old after hydrocortisone treatment

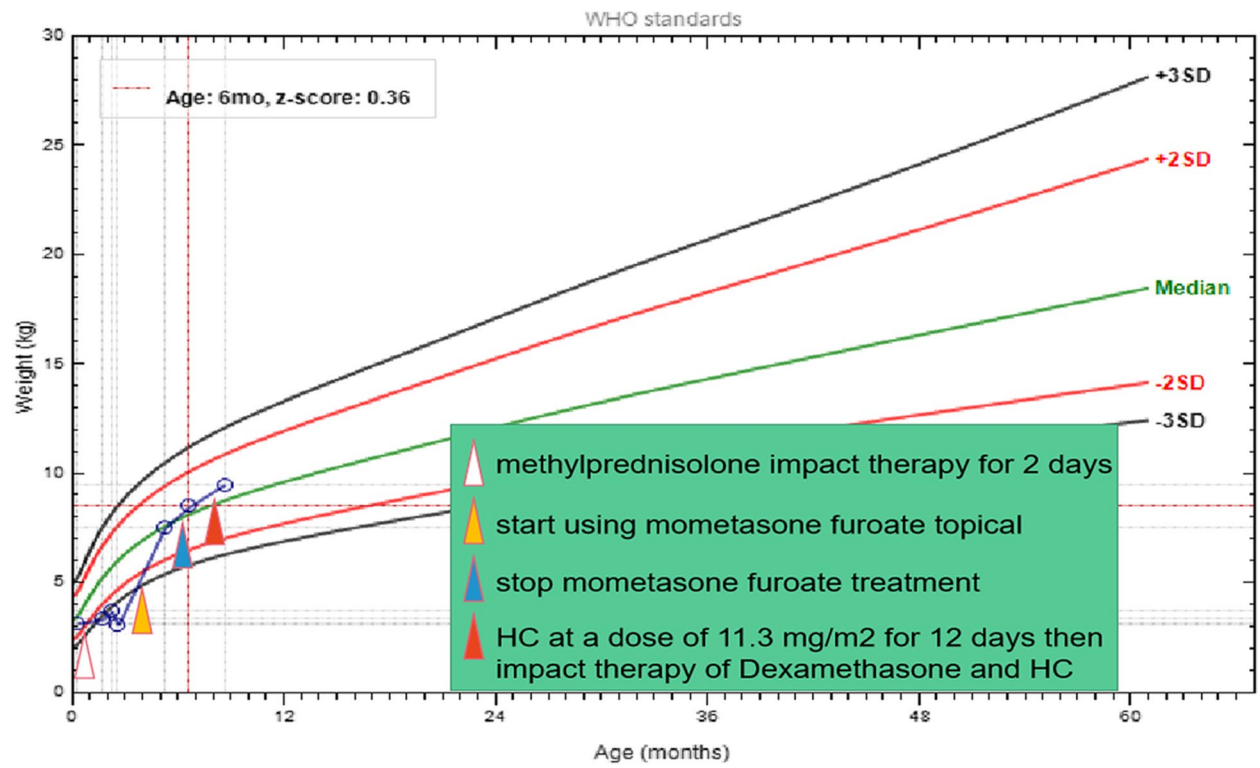

Fig. 5 The weight of patient 2 from the age of 8 days to 9 months

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/m^2/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 (sPO_2), 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 GRα 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 postreceptor 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 Bcl1; 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 clincal-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

Table 2 The data of the cases with PGGH available in the literature

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 (Patient 1)	3.6	M	Chinses	+	+	central obesity, hirsutism, moon face, acne, buffalo hump, fatigue, decreased cognitive ability, hypertension	0.00–117.27	0.00–4.35	undetectably low	normal	mifepristone	remission
	2 (Patient 2)	0.55	M	Chinses	+	+	central obesity, moon face, acne, buffalo hump, hypertension	11.51–40	<1.00		normal	no	death
Russcher et al. [3]	3	13	F	Netherlander	–	+	obesity, fatigue, growth retardation, violaceous striae, osteopenia	<30		<3.00	normal	stop using budesonide	spontaneous remission
Newfield et al. [5].	4	10.8	F	Americian	–	–	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. [4].	5	9	F	Greek	–	–	central obesity, moon face, buffalo hum, violaceous striae, acanthosis nigricans, hirsutism	0.45–7.79	1.00	9.00	normal	no	spontaneous remission
Su, et al. [6]	6	child	NM	Chinses	–	–	central obesity, moon face, buffalo hum, violaceous striae, hirusm, hypertension, growth retardation, ostalgia	Low	Normal	Low	normal	NM	NM

Table 2 (continued)

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. [14]	7	54	M	Japanese	+	–	central obesity, moon face, buffalo hump, DM	20.00 ± 19.00	<2.00	40.00–50.00	normal	NM	NM
Krysiak et al. [21]	8	28	F	Polish	–	–	Obesity, hypertension, prediabetes, osteopenia	120.31	<2.00	272.4–317.8	adrenal gland atrophy	ketoconazole, cabergoline	death because of an accident
Liu., et al. [22]	9	27	M	Chinses	+	–	central obesity, moon face, buffalo hum, violaceous striae, osteopenia	10.75	<0.22	11.95	adrenal gland atrophy	mifepristone	remission
	10 (father of case 9)	adult	M	Chinses	+	–	hypertension, moon face, buffalo hum, violaceous striae, osteopenia, hyperglycemia	NM	< 0.22	23.62	normal	no	exacerbation
Al-Shoumer, et al. [23]	11	32	F	Kuwaitis	–	+	obesity, moon face, buffalo hum, violaceous striae, DM, renal calculus, myasthenia, hypertension,	28	< 1.00	undetectably low concentration	adrenal myelolipoma	NM	NM
Zhang, et al. [1]	12	29	M	Chinses	–	–	central obesity, moon face, buffalo hum, violaceous striae, acne, osteopenia, hypokalemia, impaired glucose tolerance, hypertension	72.64–216.56	5.60–9.56	378.12	normal	no	spontaneous remission

Table 2 (continued)

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
Santen, et al. [17]	13	46	F	Americian	+	+	obesity, moon face, fatigue, headache, abdominal pain, nausea, diarrhea, anxiety/depression, muscle and joint aches, hypertension	63.00–98.00	NM	276.00	NM	no	NM

GC Glucocorticoid, *F* Female, *M* Male, *DM* Diabetes mellitus, *NM* No mention

increases the knowledge of the clinical manifestations of and the treatment experience in PGGH.

Abbreviations

ACTH: Adrenocorticotropin 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; MRIMagnetic 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-hydroxyprogesterone.

Acknowledgments

The authors would like to thank all the patients and their families for their participation in this study.

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.

Funding

This research was funded by Shenzhen Fundamental Research Program (KCXFZ20201221117340002) and Guangdong provincial high-level clinical key specialty project (SZGSP012). The funding of Guangdong provincial high-level clinical key specialty project was given the support in the analysis and interpretation of data. The funding of Shenzhen Fundamental Research Program was given the support in the collection data and writing the manuscript.

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

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

Received: 24 May 2022 Accepted: 29 October 2022
Published online: 08 November 2022

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, Grobbee 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, Jewell CM, Yudt MR, Bofetiado 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, Jewell CM, Bienstock 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 Gluconeogenesis and Inflammation in Mouse Liver. Mol Cell Biol. 2015;36:714–30.
11. Iida S, Nakamura Y, Fujii H, Nishimura J, Tsugawa M, Gomi M, et al. A patient with hypocortisolism and Cushing's 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, Lamprokostopoulou A, Polyzos A, Kino T, Katsantoni E, Triantafyllou P, et al. Transient generalized glucocorticoid hypersensitivity. Eur J Clin Investig. 2015;45:1306–15.
14. Charmandari E, Ichijo T, Jubiz W, Baid S, Zachman K, Chrousos GP, 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, Jewell CM, Yue W, Heitjan 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 KR, van Rossum EF, Ventz M, Diederich S, Quinkler M. BclI 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, Doi 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.

Publisher's Note