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Idiopathic central precocious puberty with Prader–Willi syndrome: pubertal development with discontinuation of gonadotropin-releasing hormone analog

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Summary

Prader–Willi syndrome (PWS) is a genetic imprinting disorder that is characterized by obesity, short stature, and hypogonadism. Hypogonadism is characterized by normal luteinizing hormone (LH), high follicle-stimulating hormone (FSH), low testosterone, low inhibin B, and relatively low anti-Müllerian hormone (AMH). Only a few cases of central precocious puberty (CPP) have been reported in PWS, and follow-up for CPP with PWS is not established. Hence, we present a boy with PWS accompanied by CPP. Gonadotropin-releasing hormone analog (GnRHa) therapy was started at 7 years of age, CPP was adequately arrested, and GnRHa therapy was discontinued at 11.3 years of age. Growth hormone (GH) therapy was started at 12 years of age due to inadequate growth. He grew close to his final height, and his testes developed with normal LH, increased FSH, normal testosterone, and reduced AMH corresponding to puberty at 13.5 years of age. The features of 16 patients with PWS with CPP, including our patient, were summarized. Out of seven male patients, five were treated with GnRHa, as well as four out of nine female patients. Out of 16 patients, 6 were assessed with pubertal development over 13 years of age. Pubertal development was considered to be restored in four patients who had GnRHa therapy discontinuation. We should carefully follow-up on pubertal development in CPP. GnRHa therapy is useful for adequate puberty blockage, and pubertal development could be restored with GnRHa therapy discontinuation.

Learning points:

- Pubertal development in Prader–Willi syndrome (PWS) varies from hypogonadism to precocious puberty.
- Pubertal development assessment based on clinical features and hormone levels is needed in central precocious puberty (CPP) treatment with PWS.
- Gonadotropin-releasing hormone analog (GnRHa) therapy is useful for CPP with PWS, and pubertal development can be restored with GnRHa therapy discontinuation.

Background

Prader–Willi syndrome (PWS) is a common obesogenic syndrome caused by the absence of the expression of paternally active genes on chromosome 15q11–q13. Hypogonadism is one of the main clinical features of PWS, which is characterized by normal luteinizing hormone (LH), high follicle-stimulating hormone (FSH),

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low testosterone, low inhibin B, and relatively low anti-Müllerian hormone (AMH) levels compared with those in normal males, which suggest both hypothalamic and primary hypogonadism (1). A few cases of central precocious puberty (CPP) with PWS have been reported. Although loss-of-function mutations of the makorin RING finger protein (*MKRN3)* gene at 15q11–q13 are responsible for familial CPP (2), the pathophysiology of CPP with PWS remains unknown (3). The gonadal function of CPP with PWS who received gonadotropin-releasing hormone analog (GnRHa) therapy has not fully been identified.

This article aims to reveal the pubertal development with GnRHa therapy discontinuation in patients with CPP with PWS.

Case presentation

Our patient was born at 37 weeks of gestation weighing 1944 g to a healthy Portuguese mother and a Brazilian father and displayed poor feeding, poor weight gain, and hypotonia during the neonatal period. He visited our hospital due to obesity and cryptorchidism at 3 years of age. Bilateral orchidopexy was performed. Afterward, he did not visit our hospital for a while.

He was referred to our hospital due to precocious puberty at 7.2 years of age. His height, height SDS, weight, BMI, and BMI SDS were 115.0 cm, −1.4 SDS, 26.0 kg, 19.7 kg/m^2, and +1.6 SDS, respectively. His hands and feet were relatively small, and his skin color was transparent. His bilateral testicular volume was 6 mL, with Tanner stage 3 pubic hair.

Investigation

His bone age was 12.5 years according to the Greulich and Pyle method. A GnRH test revealed pubertal LH and FSH levels (basal, peak: 0.5, 29.7 mIU/mL and 5, 22.6 mIU/mL, respectively) and testosterone was 0.41 ng/mL. Adrenal hyperplasia was excluded, although 17-hydroxyprogesterone (17-OHP), DHEA sulfate, and urinary pregnanetriolone levels were 2.7 (normal: 0.93 ± 0.81) ng/mL, 1990 (normal: 52–1080) ng/mL, and 0.034 (normal: 0.000–0.038) mg/gCr, respectively. Adrenocorticotrophic hormone test was not be performed for high 17-OHP. Abdominal CT did not detect a tumor in the adrenal gland, liver, or testis. Brain MRI did not reveal an enlarged pituitary gland. He had never been prescribed steroid hormone and had never received radiation. He was diagnosed with idiopathic CPP.

Treatment

The patient was prescribed a GnRHa (leuprorelin acetate of 0.94 mg s.c. injection every 1 month) because his bone age accelerated for his chronological age. During therapy, his testicular volume reduced in size (2 mL), LH and testosterone were suppressed, and bone age stagnated (Fig. 1 and Table 1).

Outcome and follow-up

PWS was suspected because of his history and developmental deficits at 10 years of age. Chromosome 15q11.2 deletion was identified using the fluorescent *in situ* hybridization analysis. GnRHa therapy was discontinued at 11.3 years of age because pubertal progression could be adequately suppressed and primary hypogonadism was of concern attributable to PWS. His right and left testicular volume was 3 mL and 4 mL, respectively, and bone age was 13.0 years 2 months after discontinuation (Table 1). Additionally, hormonal examination was evaluated 2 months after GnRHa therapy discontinuation and revealed the following: GnRH test demonstrated prepubertal levels of LH and FSH (peak; 6.9 mIU/mL and 7.3 mIU/mL, respectively); human chorionic gonadotropin (hCG) test showed normal testosterone levels (basal and peak; 0.17 ng/mL and 2.98 ng/mL, respectively); and AMH level was slightly low (22 ng/mL) for his prepubertal stage according to his LH level on the GnRH test (Table 1). His pituitary gland was slightly small for his chronological age on brain MRI.

His inadequate growth became remarkable (height: 130.2 cm, −2.0 SDS) at 11.3 years of age. The insulin test suggested growth hormone (GH) deficiency (basal and peak: 0.06 ng/mL and 1.07 ng/mL, respectively) at 11.5 years of age. GH therapy (0.23 mg/kg/week) was started at 12.0 years of age (height: 133.4 cm, −2.1 SDS). He grew close to his final height of 146.5 cm (−3.2 SDS) at 15.1 years of age. The right and left testicular volume was 10 mL and 15 mL, respectively, with Tanner stage 5 pubic hair and LH, FSH, testosterone, and AMH levels were 4.6 mIU/mL, 19.9 mIU/mL, 1.54 ng/mL, and 2.92 ng/mL, respectively (Table 1).

Similar cases were identified in published literature, and the features of 16 patients (7 male patients and 9 female patients) having PWS with CPP, including our patient, were summarized (Table 2) (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). Cases with premature adrenarche were excluded. Molecular pathogenesis was clear only in five patients. LH level was increased in 11 patients (case 1, 4, 5, 8, 10, 11, 12,

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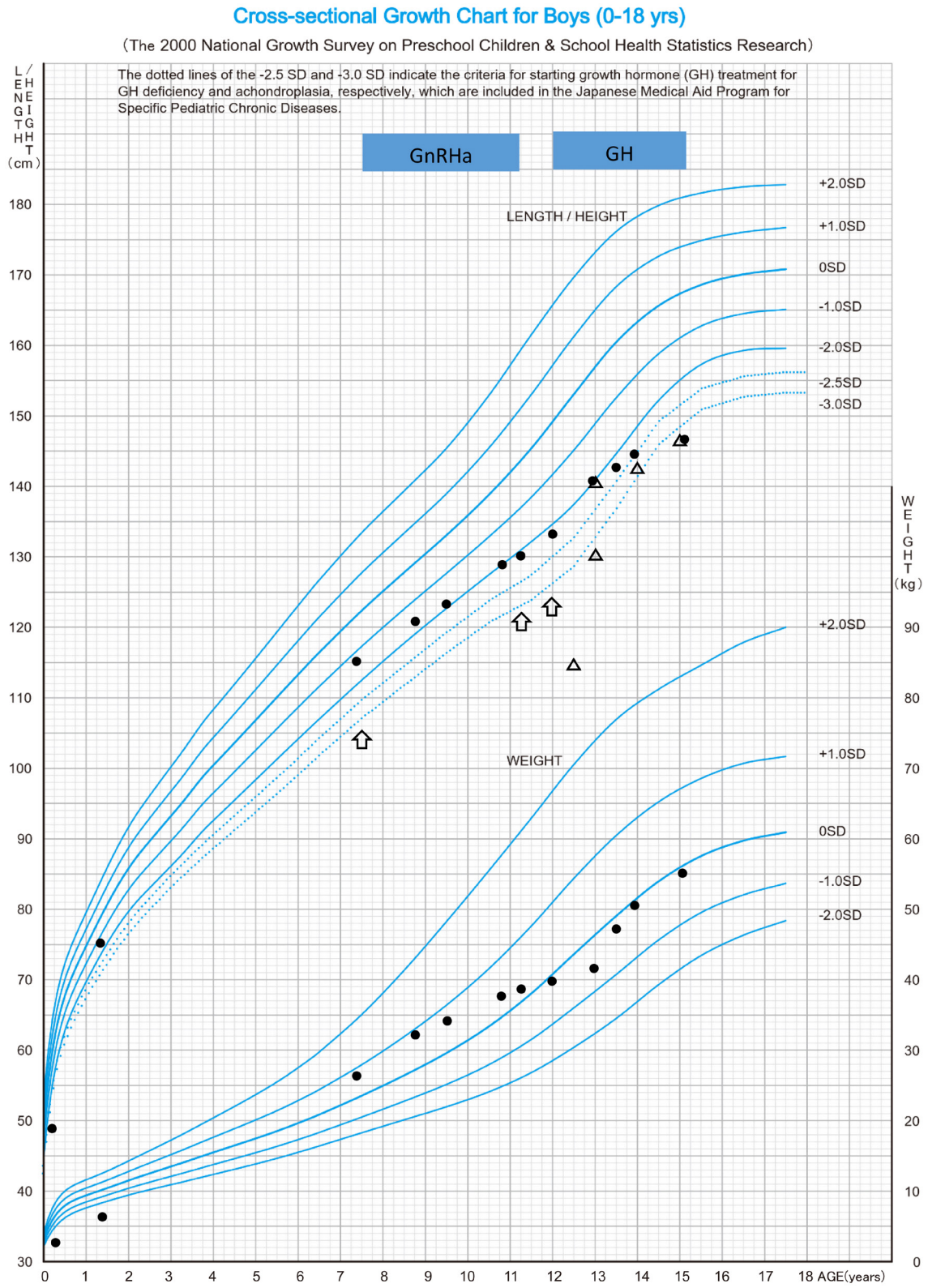

Figure 1
Growth chart of the patient on the 2000 Nation Growth Survey on Preschool Children and School Health Statics Research. Black circles represent height and weight and open triangles represent bone age. The first, second, and third arrows indicate the age at the start of GnRHa therapy, discontinuation of GnRHa therapy, and the start of GH therapy, respectively.

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Table 1 Anthropometric data, pubertal development, and hormone levels of our patient.

Age (years)	7.2	7.5 (beginning of GnRHa)	8.8	9.5	10.8	11.3 (end of GnRHa)	12.0 (beginning of GH)	12.9	13.5	13.9	15.1
Height (cm)	115.0	115.9	120.7	123.4	128.4	130.2	133.4	140.8	142.9	144.7	146.5 (final height)
Height SDS	−1.4	−1.3	−1.6	−1.8	−1.9	−2.0	−2.1	−1.9	−2.2	−2.4	−3.2
Weight (kg)	26.0	26.5	32.0	34.2	37.3	38.9	39.7	41.5	47.0	50.3	55.2
BMI (kg/m^2)	19.7	19.8	22.0	22.5	22.6	22.9	22.3	20.9	23.0	24.0	25.7
BMI SDS	1.6	1.6	1.7	1.7	1.5	1.5	1.2	0.7	1.1	1.3	1.5
Testicular volume; right/left (mL)	6/5		5/5	5/5	2/2	3/4	5/7		10/15	10/15	10/15
Pubic hair (Tanner stage)	3		3	3	3	2–3	2–3	3	3–4	4	5
LH basal (mIU/mL)	0.5		<0.1	0.2	<0.1	0.3	3.3	4.2	4.1	5.0	4.6
LH peak (mIU/mL)	29.7					6.9					
FSH basal (mIU/mL)	5		0.3	0.4	0.6	1.6	5.4	14.9	16.2	18.3	19.9
FSH peak (mIU/mL)	22.6					7.3					
Testosterone basal (ng/mL)	0.41		0.26	0.15	0.21	0.17	0.74	2.37	2.33	1.99	1.54
Testosterone peak (ng/mL)						2.98					
AMH (ng/mL)						22			2.92		
IGF-I (ng/mL) (reference range)							156 (125–557)		676 (133–579)	624	657
Bone age (years)	12.5					13.0		13.0	14.0		15.0

SDS according to the calculated chronological age using the Cross-Sectional Growth Chart for Boys (The 2000 National Growth Survey on Preschool Children and School Health Statistics Research). LH basal/peak prepubertal (≥10 years) was 0.04–0.25/2.03–11.8; FSH basal/peak prepubertal (≥10 years) was 0.01–0.25/5.69–16.6; LH basal/peak pubertal was 0.44–3.53/10.9–39.5; FSH basal/peak pubertal was 1.73–8.22/1.68–17.3; testosterone peak pubertal was >3.0 ng/mL; AMH was 5–12 years; Tanner 1 was 72.3 ± 38.5 ng/mL in >10 years; Tanner 2 was 34.9 ± 17.6 ng/mL in >10 years; Tanner 3 was 13.7 ± 9.1 ng/mL; and Tanner 4 and 5 or adult was 5.9 ± 5.3 ng/mL.

AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GnRHa, gonadotropin-releasing hormone analog; IGF-I, insulin-like growth factor I; LH, luteinizing hormone.

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Table 2 Features of 16 patients having PWS with CPP.

Reference	Case	Sex	Age of CPP onset (years)	Molecular pathogenesis (diagnostic method)	Clinical features	Growth spurt	BMI (kg/m²)	LH base, peak (mIU/mL)	FSH base, peak (mIU/mL)	Teststerone (ng/mL) or estradiol (pg/mL)	Bone age (chronological age) (years), acceleration of bone age	MRI findings, swelling of pituitary gland	GnRHa therapy, treatment period (years)	Age at last visited (years)	Pubertal development	GH therapy
Our patient	1	M	7.2	Deletion (FISH)	Increase of testicular volume (maximum 6 mL), pubic hair	Without	19.6	0.5, 29.7	5.0, 22.6	0.41	12.5 (7.2), with	Normal, without	With, 7.5–11.3	15.1	Bone age 15 years at 15.1 years, testicular volume 10 and 15 mL, Tanner stage 5 pubic hair, LH/FSH 4.6/19.9 mIU/mL, testosterone 1.54 ng/mL	With
MacMillan *et al.* (4)	2	F	6.3	Not mentioned	Breast enlargement, pubic hair	Without	40.2	Not mentioned			11 (6.3), with	Not mentioned	Not mentioned	10	Sexual maturation was slow and menstruation has not been occurred	Not mentioned
Kauli *et al.* (5)	3	F	9.5	Not mentioned	Menarche	Not mentioned	Not mentioned	Not mentioned			Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Vanelli *et al.* (6)	4	M	8.5	Not mentioned	Increase of testicular volume (maximum 10 and 12 mL)	With	Not mentioned	25 (peak)	15 (peak)	7.5	Without	Not mentioned	Not mentioned	13	Testicular volume 10 and 12 mL, Tanner stage 4 pubic hair, Tanner stage 3 axillary hair	Not mentioned
Linnemann *et al.* (7)	5	M	6.6	Deletion (G-band)	Increase of testicular volume (maximum 6 mL), pubic hair	With	43.8	0.5, 5.0	1.6, 3.6	0.69	9.1 (6.6), with	A flat pituitary gland, without	Without	Not mentioned	Testicular volume and pubic hair developed slowly	Not mentioned
Tauber *et al.* (8)	6	F	7	Deletion or abnormal methylation or uniparental disomy or no molecular anomaly	Not mentioned	Not mentioned	Not mentioned	Not mentioned			Not mentioned	Not mentioned	Not mentioned	Not mentioned	Incomplete	With
	7	F	7		Not mentioned			Not mentioned					Not mentioned			With
	8	M	9		Tanner stage 2			LH/FSH ratio on GnRH test >1		2.8			With, not mentioned			Without
	9	F	7		Tanner stage 2			Not mentioned					With, not mentioned			Without
Crino *et al.* (9)	10	F	7.4	Methylation or FISH	Not mentioned	With	34.4	Within the pubertal range on GnRH test		Within the pubertal range	With	Empty sella (in one female), not mentioned	With (in one female and one male), not mentioned	10.4	Tanner stage 3 breast, Tanner stage 2 pubic hair	Not mentioned
	11	F	7.2				35.9							13.8	Tanner stage 4 breast and pubic hair, menstruation at 10.2 years	
	12	M	8				24.7							10.6	Tanner stage 2 male genitalia, Tanner stage 3 pubic hair	
Crino *et al.* (10)	13	M	8.8	Deletion (methylation and FISH)	Tanner stage 2	With	26.2	0.4, 15.3	5.8, 10.9	2.01	10.6 (8.8), without	Gliottic ischemic damage of sub-cortical parieto-occipital area and anterior pituitary gland, without	With, 8.9–11.3	16.3	Testicular volume 10 mL, Tanner stage 3 male genitalia, Tanner stage 4 pubic hair, LH/FSH on GnRH test 31.52/40.3 mIU/mL, testosterone 1.56 ng/mL, inhibin B 4 ng/mL	With
Pusz *et al.* (11)	14	F	5	Maternal uniparental disomy	Breast enlargement, pubic hair	With	22.9	4.6 (base)	14.8 (base)	23	13.6 (9.4), with	Not mentioned	With, 8.8 and not mentioned	14.4	With discontinuation of GnRHa menstruation began, Tanner stage 3 breast, Tanner stage 4 pubic hair	With
Lee *et al.* (12)	15	F	8.2	Deletion (methylation and FISH)	Breast enlargement, pubic hair	With	17.2	1.0, 10.3	1.7, 9.2	15	10.5 (8.2), without	Not mentioned	With, 8.3 and still receiving	9.5	Tanner stage 2	With
Ludwig *et al.* (13)	16	M	8	Hypermethylation	Tanner stage 2	With	21.3	0.5, 15.8	5.6 (base)	0.13	9.9 (8.0), without	Normal, not mentioned	With, 8.8–13	15.2	Tanner stage 3 male genitalia, testicular volume 3 mL, LH/FSH <0.07/0.15 mIU/mL, testosterone 0.14 ng/mL at 14.3 years of age, Tanner stage 4 male genitalia, testicular volume 5 and 6 mL	With

CPP, central precocious puberty; FSH, follicle-stimulating hormone; GH, growth hormone; GnRHa, gonadotropin-releasing hormone analog; LH, luteinizing hormone; PWS, Prader–Willi syndrome.

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13, 14, 15, and 16). Nine patients were treated with GnRHa (5 male patients: cases 1, 8, 12, 13, and 16; 4 female patients: cases 9, 10 or 11, 14, and 15), two patients were not treated with GnRHa (1 male patient and 1 female patient), and five patients were not mentioned whether treated or not. Cases 1, 13, 14, and 16, who were treated with GnRHa, were assessed for pubertal development after discontinuation at 13.0 years of age or older, with Tanner stage 3 or 4 in all of them. Case 4, who was not treated with GnRHa, was assessed for pubertal development at 13.0 years of age, Tanner stage 3–4. Cases 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, and 15 were assessed for pubertal development under 13.0 years of age, and age at the last visit was not mentioned.

Out of 9 patients who were treated with GnRHa, 5 had GH therapy (cases 1, 13, 14, 15, and 16), 2 had not performed GH therapy (cases 8 and 9), and 2 patients had not mentioned GH therapy. The external genitalia development was Tanner stage 3–4 in 5 patients who were treated with GH (cases 1, 13, 14, 15, and 16); pubertal development was incomplete in 2 who were not treated with GH (cases 8 and 9).

Discussion

Here, we presented a rare case of male CPP with PWS confirmed by chromosome 15q11.2 deletion after GnRHa therapy initiation. Our patient fulfilled all CPP diagnostic criteria, that is, testicular enlargement, advanced bone age, high androgen level, and LH pubertal response to GnRH test. He also presented with PWS features, hypotonia, insufficient weight gain, and cryptorchidism in the newborn period and obesity, developmental disability, and learning disability in school age. However, the absence of short stature and delayed puberty, which are characteristic manifestations of PWS, were masked by CPP.

The re-evaluated gonadal function after GnRHa therapy revealed an incomplete gonadotropin response for the GnRH test, while testosterone showed a normal response for the hCG test. . However, the gonadal function was well in LH and testosterone levels, and Sertoli cells have been kept active after GnRHa therapy because the AMH level was not significantly low. Patients with PWS commonly do not complete puberty, which may correlate with prolonged AMH activity (1).

Patient with PWS commonly have delayed or incomplete puberty, and premature adrenarche is occasionally reported with increased adrenal androgen secretion, induced by adiposity as well as healthy obese children, but true precocious puberty is extremely rare. Therefore, we identified a case series of patients with PWS who presented with CPP in the published literature and summarized the features of 16 cases, including our patient's (Table 2) (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). We could not clarify the correlation between the frequency of CPP and molecular pathogenesis because only five cases mentioned molecular pathogenesis. CPP was considered to be caused by hypothalamic–pituitary acceleration by increased LH levels in 11 patients, and 9 patients were treated with GnRHa. Four patients showed external genitalia maturation with discontinuation of GnRHa therapy; it is considered to be restored to pubertal development. And pubertal development without GnRHa therapy was confirmed in 1 patient (case 4). Pubertal development in patients with PWS with CPP is considered to be going well with or without GnRHa therapy. Furthermore, GH therapy probably may help the pubertal development after GnRHa therapy discontinuation (14, 15).

Loss-of-function mutations of the *MKRN3* gene, located on chromosome 15q11–q13 in the critical PWS region, are reported as responsible for familial CPP (2). Normally, MKRN3 is thought to prevent the onset of puberty at high levels in the brain before adolescence. A paternally derived MKRN3 allele deletion in PWS can cause puberty to start at an inappropriately young age. Alternatively, 17-hydroxyprogesterone and DHEA sulfate levels were high in our patient at CPP diagnosis, which may indicate increased adrenal androgen levels as previously reported in PWS. Thus, precocious puberty may occur in our patient as a combination of paternally derived MKRN3 allele deletion, basal adrenarche, and hypothalamic–pituitary acceleration. Other findings support the hypothesis that GnRHa therapy showed good clinical and laboratory response, that is, adequate puberty blockage evaluated by decreasing testicular volume, decreasing gonadotropin and testosterone, and bone age stabilization, which was restored after GnRHa discontinuation.

In conclusion, CPP is considered even if the patient was already diagnosed with PWS. GnRHa therapy may be beneficial, especially for male patients, because the male pubertal signs were identifiable due to the increased adrenal androgen levels in PWS as previously reported. Accumulating cases that are examined post-GnRHa gonadal function is desirable to assess the long-term effects of GnRHa therapy for CPP in PWS.

Patient's perspective

At first, his main concern was about height; thus, he and his family were cooperative about GnRHa and GH therapy. After the GnRHa treatment, he got obese and his blood glucose level gradually increased. He had a mild and obedient character, so he did not complain about final height

but felt some deal of stress on dietary restrictions. He has been followed up at the pediatric endocrinology department and was followed together with genetic counseling by pediatric psychotherapists. His quality of life is fulfilling because community health workers and school teachers support his activities.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of this article and accompanying images.

Author contribution statement

Mami Kobayashi wrote the manuscript. Hideaki Yagasaki is the primary physician of the patient. Kei Tamaru and Yumiko Mitsui managed the patient's genetic testing and treatment. Takeshi Inukai supervised and all authors approved the final version of the manuscript.

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