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ORIGINAL ARTICLE

Response to growth hormone treatment in Prader–Willi syndrome: Auxological criteria versus genetic diagnosis

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Aim: The Australian Prader-Willi Syndrome (PWS) database was established to monitor the efficacy and safety of growth hormone (GH) treatment in PWS. This study aims to compare response to GH based on eligibility criteria.

Methods: Comparative study: 72 children received GH on the basis of short stature or evidence of GH deficiency (pre-2009: PWS-SS) and 94 on a genetic diagnosis (post-2009: PWS-Dx). We report on mandatory patient data for GH prescription: median and standard deviation score (SDS) for height and body mass index (BMI), waist/height ratio, bone age/chronological age ratio and adverse events. Comparisons were made using non-parametric tests.

Results: At baseline, the PWS-SS cohort was shorter (height SDS: −2.6 vs. −1.1, $P < 0.001$), had a lower BMI (0.6 vs. 1.5 SDS, $P < 0.05$) and greater bone age delay (bone age/chronological age: 0.7 vs. 0.9, $P < 0.05$) than the PWS-Dx cohort. PWS-SS parents were shorter (mid-parental height SDS: −0.13 vs. 0.28, $P < 0.005$). Mean change in height over 2 years was 0.9 SDS and in BMI using PWS reference standards −0.3 SDS_{PWS} ($n = 106$) (year 2, height SDS: PWS-SS = −1.7, PWS-Dx = 0.1; BMI SDS_{PWS}: PWS-SS = −1.0, PWS-Dx = −0.6). The waist/height ratio reduced (PWS-Dx: 0.60 vs. 0.56, $P < 0.05$) and bone age delay was unchanged over this period. No serious adverse events were reported.

Conclusions: The PWS-SS cohort represents a subgroup of the wider PWS-Dx population; however both cohorts improved height SDS with normalisation of height in the PWS-Dx cohort and lowering of BMI relative to PWS standards supporting the efficacy of treatment under the current Australian GH programme.

Key words: disability; growth hormone; metabolic; obesity; Prader–Willi syndrome.

What is already known on this topic

1 Children with Prader–Willi syndrome (PWS) are short and are prone to become morbidly obese.
2 The abnormal body composition (increased fat mass and reduced lean tissue mass) in people with PWS is already present in underweight infants and resembles that of people with growth hormone deficiency.
3 Growth hormone (GH) treatment of 6–7 mg/m^2/week normalises height standard deviation score (SDS) and improves body composition in children with confirmed PWS.

What this paper adds

1 Children with PWS selected under the criteria of a genetic diagnosis or on the basis of anthropometric criteria responded equally well to GH treatment.
2 GH treatment of 4.5 mg/m^2/week improved height SDS of children with a genetic diagnosis of PWS without accelerating skeletal maturity or causing serious adverse events over a 2-year period.
3 GH treatment of 4.5 mg/m^2/week improved the body composition of children with a genetic diagnosis of PWS, highlighting the metabolic benefits of GH treatment in children with PWS.

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Prader–Willi syndrome (PWS) is a complex genetic condition caused by a lack of expression of imprinted genes on paternally derived chromosome 15q11-13 and is characterised by short stature and an abnormal body composition (low lean tissue mass and increased fat mass) attributed to hypothalamic dysfunction.[1–4] Growth hormone (GH) treatment improves linear growth of children with PWS and increases the proportion of lean to fat mass as well as bone mineral density.[5–8]

In 2009, a new set of eligibility criteria was approved such that children genetically diagnosed with PWS could receive subsidised GH treatment in Australia under the Pharmaceutical Benefit Scheme (PBS) GH programme until 18 years to improve height and body composition.[9] This is the first indication in Australia in which GH treatment is prescribed for reasons in addition to improvement of height, that is for its potential of a sustained beneficial effect on body composition to improve muscle mass and reduce fat mass until adulthood.[7,8] Before 2009, children with PWS obtained subsidised GH under the criteria of short stature and slow growth (SS; height <1st centile, height velocity <25th centile for bone age (BA)) or GH deficiency (GHD; peak serum GH < 10 mU/L in response to two stimulation tests). Seventy-two children with PWS received GH under these criteria between 1974 and 2009. In addition, a considerable number of children who were disqualified under these criteria obtained GH on a private script until the introduction of the new criteria in 2009. Since 2009, all children with genetically confirmed PWS are eligible for GH treatment until 18 years of age unless they have uncontrolled morbid obesity or one of the standard exclusions regarding diabetes mellitus or known risk of malignancy.[10] Because in PWS, respiratory problems (insufficiency and infections) were the predominant cause of death in children, including some children who received GH treatment,[11] the new criteria request 6 months of growth data and a sleep study within 12 months before initiation of GH treatment and one within the initial GH treatment period.

In 2008, the Australian PWS database (APWSdb) was established for long-term surveillance of efficacy and safety of GH treatment in children with PWS.

This paper introduces the APWSdb presenting a current picture of all children with PWS on subsidised GH treatment and compares the characteristics of the two cohorts of children with PWS based on eligibility criteria and their response to GH during the first 2 years of treatment under the government scheme.

Methods

The APWSdb combines deidentified patient data from the OZGROW database, which contains mandatory information requested by the government on all children treated with GH under the PBS with additional retrospective and prospective PWS specific data obtained from patients attending eight PWS hospital clinics that care for most children with PWS in Australia. Ethics approval was obtained from the participating hospitals and universities. Parental consent to participate in OZGROW and the APWSdb was obtained separately by the treating physicians.

Data collection and patients

Baseline data collected 6 months prior to and at commencement of GH treatment on the PBS included patient gender, birthweight and length, gestation period, parental height, age, height, weight, puberty (Tanner staging) and BA (Greulich and Pyle) and, since 2009, head and waist circumference. Follow-up data collected at least biannually included GH dose (mg/m^2/week) along with the above-mentioned anthropometric measurements. BA assessments are recorded annually. Adverse events are reported as they occurred. Data on puberty, spinal curvature, developmental delay, sleep studies, body composition tests and various other endocrine functions are collected but are not presented here as collection of these PWS specific data, except for puberty, only started since the introduction of PWS eligibility.

Two cohorts were defined on the basis of whether they started GH under the SS or GHD criteria (PWS-SS cohort) or the new criteria based on genetic diagnosis (PWS-Dx cohort). All children are started on a dose of 4.5 mg/m^2/week with potential to increase the dose at 6 monthly intervals to a maximum of 7.5 mg/m^2/week until BA maturity (13.5 years for females, 15.5 years for males) has been reached.[10] Increases with 1.5 mg/m^2/week are allowed when one or more response criteria, such as improvement of height centile using Centres for Disease Control (CDC 2000)[12] or PWS reference standards, body mass index (BMI) standard deviation score (SDS) (CDC 2000), waist circumference SDS, waist/height ratio or improvement in body composition are not met. The new criteria allow adolescents with a mature BA to receive an adult dose of GH (≤0.04 mg/kg/week) until 18 years of age. Overweight patients (BMI >85th centile) are dosed according to an ideal weight for height (50th centile of CDC 2000).[10] The doctor's visit date at which the GH application was made was used to obtain the baseline measurements.

Statistical analysis

Age- and gender-specific SDS for height, weight and BMI were calculated for each child using the CDC 2000 standards.[12] BMI SDS could not be calculated for children under 2 years as the CDC 2000 did not provide the necessary data. In addition, we present results using PWS specific reference standards of a genetically diagnosed population of children with PWS reported as SDS_{PWS}.[13] Unless specified, any discussion of SDS refers to the CDC 2000 standards. BA delay was represented by a ratio BA/CA < 1. Waist/height ratio was recorded for the PWS-Dx cohort only since waist circumference was not reported prior to 2009.

Data were checked for normality using the DiAgostino-Pearson omnibus test. Descriptive continuous data are reported as median and inter-quartile ranges. The two cohorts were compared using the non-parametric Mann–Whitney *U*-test, and the difference in SDS of each cohort between time points with the Wilcoxon signed rank test as in most cases data were not normally distributed. The individual mean change was compared with the Student's *t*-test.

Results

Background and baseline comparison of anthropometric data and BA

The birth characteristics of the PWS-SS cohort ($n = 72$) and the PWS-Dx cohort ($n = 94$) are presented in Table 1. Although the gestational age and birthweight were similar, birth length was significantly shorter in the PWS-SS cohort compared with the PWS-Dx group (length, 47.5 vs. 49.2 cm, $P = 0.012$). Parents of the PWS-SS cohort were also shorter than parents of the PWS-Dx cohort (parental height SDS, −0.13 vs. 0.28, $P = 0.004$).

Table 1 Background of two cohorts of children with PWS defined by the eligibility criteria for access to subsidised growth hormone treatment: PWS-SS cohort (GH access on short stature and slow growth or GH deficiency <2009) and PWS-Dx cohort (GH access on genetic diagnosis ≥2009)

	PWS-SS cohort		PWS-Dx cohort		*P* value
	Mean (SD)	*n*	Mean (SD)	*n*	
Birthweight (kg)	2.62 (0.53)	54	2.74 (0.58)	88	0.212
Birth length (cm)	47.50 (3.08)	40	49.23 (3.47)	62	**0.012**
Gestation (weeks)	38.61 (2.78)	54	37.87 (5.83)	92	0.383
Father's height SDS	–0.11 (1.00)	54	0.22 (1.02)	84	0.063
Mother's height SDS	–0.15 (1.06)	54	0.34 (1.00)	86	**0.007**
Parental height SDS	–0.13 (0.83)	54	0.28 (0.81)	84	**0.004**

Bold values are significantly different. GH, growth hormone; PWS, Prader–Willi syndrome; SD, standard deviation; SDS, standard deviation scores. *P* values determined from *t*-tests.

The PWS-SS cohort was significantly shorter (median height SDS, –2.6 vs. –1.1, $P < 0.001$), lighter (median weight SDS, –1.3 vs. 0.2, $P < 0.001$) and had a lower BMI (median BMI SDS, 0.6 vs. 1.5, $P = 0.012$) at baseline than the PWS-Dx cohort (Table 2). Compared with PWS reference standards, the median height, weight and BMI of the PWS-Dx cohort at baseline was similar to that expected for PWS patients (SDS_{PWS} 0.2, 0.1 and 0.0, respectively), whereas those of the PWS-SS cohort (SDS_{PWS} –0.8, –0.8 and –0.4, respectively) were all lower ($P < 0.001$, Table 2). BA was significantly more delayed in the PWS-SS cohort than in the PWS-Dx cohort at baseline (BA/CA, 0.7 vs. 0.9, $P = 0.018$) (Table 2).

The median age of children who commenced GH treatment on the PBS and the mean dose of GH received over the period of assessment did not differ significantly between the two cohorts (Table 2).

Height, BMI, waist/height ratio and BA/CA during GH treatment

Figure 1 shows the change in height SDS of both cohorts over the period of GH treatment. We compared the difference in the median height, weight and BMI SDS of the two cohorts using only the individuals who completed 2 years of treatment. The median height SDS of the PWS-SS cohort increased from –2.6 to –1.7 SDS ($n = 66$, $P < 0.001$). In the same period, the median height of the PWS-Dx cohort normalised from –0.8 to +0.1 SDS ($n = 40$, $P < 0.001$).

The overall individual mean change in height SDS over the 2 years was 0.9 SDS (standard deviation (SD) = 0.8, $n = 106$). The greatest change was by the short stature cohort (PWS-SS = 1.1, SD = 0.8, $n = 66$; PWS-Dx = 0.5, SD = 0.7, $n = 40$, $P < 0.001$). However, the Dx cohort included 12 patients who had previously purchased GH privately (baseline at start of subsidised GH was 0.1 height SDS and mean height change 0.2 SDS, SD = 0.4), the mean 2-year change in height of the Dx cohort minus the 12 patients we retrospectively identified as not naive to GH or patients with a mature BA on adult dose was 0.7 SDS, SD = 0.8, $n = 27$, $P = 0.035$.

After 2 years of GH treatment, the BMI SDS no longer differed between the two cohorts (Table 2). Although the BMI SDS of both cohorts were above the average of the normal population and did not significantly differ from base line (CDC 2000 standard), they had reduced to well below the mean of the PWS reference standard (PWS-SS; from –0.4 to –1.0 SDS_{PWS}, $n = 66$, $P < 0.001$ and PWS-Dx; from –0.3 to –0.6 SDS_{PWS}, $n = 40$, $P < 0.005$). Figure 2 presents the decline of the PWS specific BMI SDS_{PWS} of both cohorts. The mean individual change was –0.3 SDS_{PWS}, (SD=0.6, $n = 106$). Excluding children under 2 years who may have been underweight gave a similar result (–0.3 SDS_{PWS}, SD=0.6, $n = 95$).

The median waist/height ratio, measured in the PWS-Dx cohort only, was 0.60 at baseline and 0.53 after 2 years of GH treatment (Table 2). The reduction in individuals with measurements at baseline and year 2 was significant (0.60 vs. 0.56, $n = 16$, $P = 0.04$; 1st year, 0.60 vs. 058, $n = 39$, $P < 0.001$; 2nd year, not significant).

After 2 years of treatment, the BA of the PWS-SS cohort remained significantly more delayed than the BA of the PWS-Dx cohort (BA/CA, 0.8 vs. 1.0, $P = 0.04$, Table 2).

Adverse events

In five children, aged 2–5 years, GH treatment was suspended 3–18 months after starting treatment due to alterations in respiratory function. Four resumed GH treatment after 3–11 months and one after 28 months (one had the settings of the variable positive airway pressure machine adjusted and four were referred for tonsillectomy or adenoidectomy). Treatment was ceased in a 16.5-year-old girl because of non-compliance due to behavioural problems and weight increase with respiratory concerns. In one case, initiation of GH treatment was delayed for 5 months with no reason given.

Discussion

The establishment of genetic eligibility criteria for GH treatment of children with PWS in Australia provided a unique opportunity to examine the efficacy and side effect profile of GH therapy in this large cohort of 166 individuals. As an initial step, we characterised the two cohorts defined by the eligibility criteria (PWS-SS vs. PWS-Dx) and then compared their response to GH treatment. This report highlights several differences between the two cohorts.

Firstly, the PWS-SS cohort who had received GH under anthropometric criteria or because of GHD was shorter at birth and had shorter parents than the PWS-Dx cohort. This suggests, *a priori*, a reduced genetic height potential in addition to having short stature as a consequence of PWS. At baseline, this cohort was shorter and had a lower BMI and greater BA delay than the PWS-Dx cohort, which resembled a typical genetic reference population of PWS as described by Hauffa *et al*.[13] After 2 years of GH treatment, the height SDS of the PWS-SS cohort improved but was still below normal (–1.7 SDS). In contrast, the height SDS of the PWS-Dx cohort normalised to +0.1 SDS (CDC 2000) in this period (Fig. 1).

The overall mean individual change in height was 0.9 SDS. The mean individual change in height of the SS cohort of 1.1

Table 2 A comparison of height, weight and BMI standard deviation scores using normal (CDC 2000) and PWS specific reference standards, the ratio of bone age/chronological age and waist/height of two cohorts of children with PWS defined by the eligibility criteria for access to subsidised GH treatment at baseline, after 1 and after 2 years of treatment: PWS-SS cohort (GH access on short stature and slow growth or GH deficiency <2009) and PWS-Dx cohort (GH access on genetic diagnosis ≥2009). Waist circumference was not measured in the PWS-SS cohort

		PWS-SS cohort of PWS		PWS-Dx cohort		*P* value
		Median (Q1 to Q3)	*n*	Median (Q1 to Q3)	*n*	
Baseline	Age at start GH (years)	4.8 (2.7 to 9.7)	72	3.9 (2.0 to 10.1)	94	0.170
	Male/female		38:34		46:48	
	Height SDS†	–2.6 (–3.1 to –2.2)	72	–1.1 (–2.0 to –0.5)	94	**<0.001**
	Height SDS_{PWS}‡	–0.8 (–1.3 to –0.5)	72	0.2 (–0.2 to 0.9)	94	**<0.001**
	Weight SDS	–1.3 (–2.7 to –0.7)	72	0.2 (–1.1 to 1.3)	94	**<0.001**
	Weight SDS_{PWS}	–0.8 (–1.4 to –0.4)	72	0.1 (–0.5 to 0.8)	94	**<0.001**
	BMI SDS	0.6 (–0.2 to 1.8)	64	1.5 (0.5 to 2.2)	72	**0.012**
	BMI SDS_{PWS}	–0.4 (–1.2 to 0.1)	72	0.0 (–0.7 to 0.8)	94	**<0.001**
	BA/CA	0.7 (0.6 to 0.8)	66	0.9 (0.6 to 1.0)	73	**0.018**
	Waist/Height			0.60 (0.57 to 0.64)	62	
1 year GH	Height SDS	–1.9 (–2.4 to –1.3)	68	–0.8 (–1.4 to 0.0)	66	**<0.001**
	Height SDS_{PWS}	–0.4 (–0.9 to 0.1)	68	0.6 (0.1 to 1.1)	66	**<0.001**
	Weight SDS	–0.8 (–1.9 to –0.1)	68	0.4 (–0.6 to 1.3)	66	**<0.001**
	Weight SDS_{PWS}	–0.7 (–1.4 to –0.3)	68	0.0 (–0.5 to 0.4)	66	**<0.001**
	BMI SDS	0.4 (–0.5 to 1.5)	67	1.2 (0.7 to 1.9)	57	**0.005**
	BMI SDS_{PWS}	–0.9 (–1.6 to –0.2)	68	–0.3 (–1.0 to 0.4)	66	**0.001**
	BA/CA	0.7 (0.6 to 0.9)	36	0.9 (0.8 to 1.0)	44	**0.002**
	Waist/height			0.56 (0.52 to 0.59)	65	
	Mean GH dose (mg/m^2/wk)	4.5 (4.2 to 5.0)	68	4.5 (4.2 to 4.7)	66	0.527
2 years GH	Height SDS	–1.7 (–2.1 to –1.0)	66	0.1 (–1.2 to 0.4)	40	**<0.001**
	Height SDS_{PWS}	–0.2 (–0.6 to 0.3)	66	0.9 (0.3 to 1.4)	40	**<0.001**
	Weight SDS	–0.4 (–1.5 to 0.9)	66	0.8 (0.1 to 1.5)	40	**<0.001**
	Weight SDS_{PWS}	–0.7 (–1.2 to 0.0)	66	–0.1 (–0.5 to 0.3)	40	**0.001**
	BMI SDS	0.8 (–0.3 to 1.9)	66	1.0 (0.4 to 1.9)	40	0.218
	BMI SDS_{PWS}	–1.0 (–1.5 to 0.0)	66	–0.6 (–1.4 to 0.2)	40	0.204
	BA/CA	0.8 (0.7 to 1.0)	37	1.0 (0.8 to 1.1)	31	**0.040**
	Waist/height			0.53 (0.49 to 0.62)	47	
	Mean GH dose (mg/m^2/wk)	4.6 (4.2 to 5.1)	66	4.6 (4.4. to 5.3)	40	0.735

Bold values are significantly different. †SDS, standard deviation scores using CDC 2000[12]. ‡SDS_{PWS}, standard deviation scores using Prader–Willi syndrome (PWS) specific growth standards of 2000[13]. BA/CA, bone age/chronological age; BMI, body mass index; GH, growth hormone; Q_1 to Q_3, first to third quartile. *P* values determined using Mann–Whitney *U*-tests.

SDS was slightly greater than this as unlike the Dx cohort they had not yet normalised height. A similar increase in height over 2 years was reported from a study of German children (1.2 SDS, n = 10, age range 7–16 years) in which a comparable GH dose (4.7 mg/m^2/week)[14] was used and from a French study (1.1 SDS, $n = 36$, age range 1–15) in which children received a higher mean GH dose of 0.033 mg/kg/day (approximately 6–7 mg/m^2/week).[15] However, a greater increase in height (1.67 SDS) was reported from a Dutch study using a higher mean dose of 7 mg/m^2/day.[8] The German study included patients with PWS on the basis of GHD, whereas the latter two studies included patients on the basis of genetic diagnosis of PWS.

The PWS-Dx cohort normalised height more rapidly than in some other studies where this was attained in 3–4 years.[8,15,16] However, it should be noted that baseline height SDS in these studies (−1.8 to −2.3 SDS) was generally lower than in our cohort. Several factors contributed to the taller stature of the current PWS-Dx cohort at baseline (−1.1 SDS). Firstly, very short children born before 2009 would have started GH treatment under the previous criteria of short stature or GHD and are thus represented in the PWS-SS cohort. Secondly, we retrospectively identified 12 patients who started GH under the new genetic eligibility criteria (PWS-Dx cohort) but whose parents had previously purchased GH privately as their children had been disqualified under one of the previous criteria for access to GH. These patients had already normalised their height (median height +0.2 SDS, range −0.1 to 0.5) on starting GH treatment under the government programme, slightly skewing the baseline of the Dx cohort (median height SDS-1.3, n = 82 excluding these 12 patients). The observation that the current PWS-Dx cohort at baseline is relatively taller compared with other international PWS cohorts may thus be a transient situation.

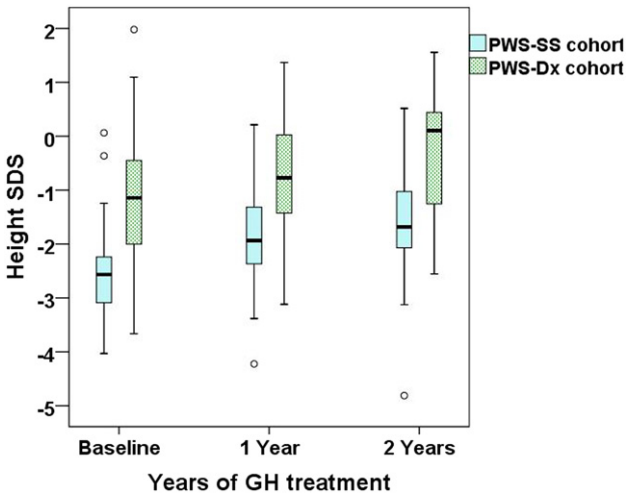

Fig. 1 Box plots of the height standard deviation scores (SDS) using the CDC 2000 reference standards of two cohorts of children with PWS defined by the eligibility criteria for access to growth hormone treatment at baseline, after 1 and after 2 years of treatment: PWS-SS cohort (GH access on short stature and slow growth or GH deficiency <2009) (open bars) and PWS-Dx cohort (GH access on genetic diagnosis ≥ 2009) (dotted bars), explanation as in Table 2. □, PWS-SS cohort; ▨, PWS-Dx cohort.

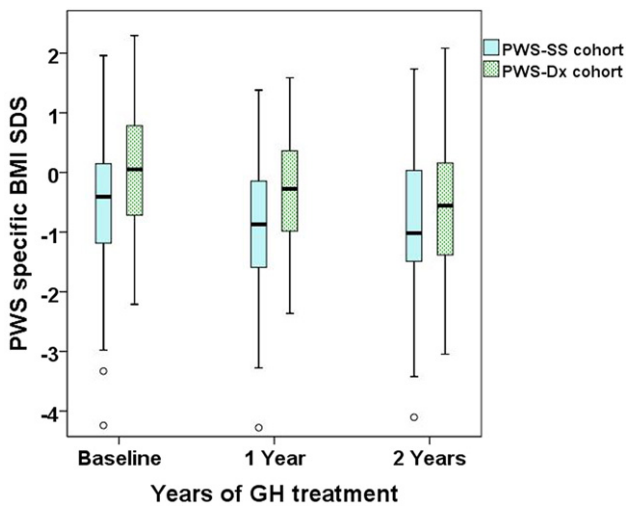

Fig. 2 Box plots of BMI standard deviation scores (SDS) using the PWS specific reference standards of two cohorts of children with PWS defined by the eligibility criteria for access to growth hormone treatment at baseline, after 1 and after 2 years of treatment: PWS-SS cohort (GH access on short stature and slow growth or GH deficiency <2009) (open bars) and PWS-Dx cohort (GH access on genetic diagnosis ≥ 2009) (dotted bars), explanation as in Table 2. □, PWS-SS cohort; ▨, PWS-Dx cohort.

Since 1999, at least 21 families purchased GH for their children, who had been disqualified under the criteria of the government programme, until this became available in 2009 for those who were still under 18 years. Initially, the documented benefits of GH treatment of normalisation of height and improvements in physical ability, strength, endurance and possibly behaviour of children with PWS,[2,16,17] as well as endorsement on genetic basis of PWS by the Food and Drug Administration in the USA in June 2000,[18] were important factors contributing to the family's decision to purchase GH privately. In later years, perceived benefits of reaching developmental milestones earlier and improving cognitive or mental development[19,20] may have contributed to the growing number of families privately obtaining GH for their children.

BA was more delayed in the PWS-SS cohort than the PWS-Dx cohort when compared with chronological age both at baseline (BA/CA = 0.7 vs. 0.9) and after 2 years of GH treatment (BA/CA = 0.8 vs. 1.0). As observed in earlier studies,[14,16] BA did not advance beyond CA despite substantial catch up growth in both cohorts during the treatment period suggesting final height would not be compromised.

Although the median BMI SDS of both cohorts was above the mean of the normal population after 2 years of GH treatment, it declined to well below that of the PWS reference standards, that is to −1.0 SDS_{PWS} (PWS-SS) and −0.6 SDS_{PWS} (PWS-Dx), suggesting that GH may prevent or lessen the increase in BMI normally associated with the growth trajectory of children with PWS.[13] A similar trend of decline but not normalisation of BMI has been observed in other studies.[21,22] A significant reduction was also noted in the waist/height ratio of the PWS-Dx cohort during the first year of GH, which was maintained in the second year. The reduction in BMI and waist/height ratio relative to untreated patients is very relevant given the high morbidity and mortality in PWS largely due to obesity-related complications.[4,23,24] The relative benefit of GH therapy in relation to cardiovascular and metabolic parameters as an outcome of the Australian GH programme with the currently prescribed doses is yet to be fully established and is an ongoing goal of the APWSdb. However, our data support the notion that GH therapy is effective in maintaining an improved body composition relative to children with PWS not on GH treatment.

Monitoring adverse events was one of the objectives of the APWSdb as a small number of deaths have been reported internationally in children receiving GH treatment.[25] Subsequent analyses of the cause of death in a large number of children both treated and never treated with GH failed to find evidence of a causal relationship with GH. The majority of death were due to infections of the respiratory (44%) or other system (14%).[11] Although GH treatment was temporarily suspended in five children due to respiratory problems, no major adverse events have been reported so far. With relatively small numbers, the power to identify rare adverse events is limited. As a precaution, a sleep study is mandatory under the new criteria, and respiratory problems must be addressed before commencement of GH. The obligatory preliminary sleep study has the benefit to diagnose obstructive sleep apnoea especially in older children who did not have obvious symptoms of sleep disordered breathing.[26] In addition, a sleep study must be repeated within 6 months of commencing GH treatment. Concern that adrenal insufficiency may contribute to some cases of sudden death has been raised.[27,28] However, further research in adrenocorticotropic hormone deficiency showed that central adrenal insufficiency could be considered uncommon in PWS and, in Australia, testing is recommended to be done on a case-by-case basis.[29]

Extensive follow-up is being undertaken to detail any adverse effects that may be associated with the current GH treatment programme.

A limitation of this initial report is that to fully characterise the data in the APWSdb, we reported on all patients receiving GH as reported by the Department of Health and Ageing to the OZGROW database. We note the following heterogeneity of patients in the PWS-Dx cohort as a result of the change in GH eligibility criteria: two patients with a mature BA, who received an adult dose of GH (≤0.04 mg/kg/week), and 12 patients, who had already normalised their height and substantially improved their body composition due to purchasing GH privately before obtaining this under the PBS subsidised programme. Inclusion of these patients may have affected the baseline values of the PWS-Dx cohort while also resulting in a reduction in the mean response to GH of the PWS-Dx cohort both in terms of height and body composition. In the next few years, we anticipate including the few remaining children who transferred from private to subsidised supply and expect an increase in adolescents receiving an adult dose of GH necessitating separate analyses for these groups.

We can draw some important conclusions of the current analyses. Firstly, the PWS-SS cohort was a distinctly different subgroup of the genetic PWS-Dx cohort. Given this cohort was eligible under short stature or GHD it is expected that they respond well to GH therapy. However, as their genetic height potential was also shown to be lower, their final adult height gained would likely be less than that achieved by the PWS-Dx cohort, which normalised height during the two years of GH treatment. Secondly, despite initial differences between the cohorts at baseline, both cohorts improved BMI SDS_{PWS} when compared with PWS reference standards.[13] Given the wide variation in weight particularly in the pubescent children with PWS, the PWS specific reference standards are more appropriate in the assessment of therapeutic response in body composition than the CDC standards.

Following this preliminary study, we anticipate further analyses using the APWSdb in effectiveness-based research that will inform decisions on GH treatment such as in the appropriateness of the dose, age of initiation, adult height reached and other metabolic outcomes of GH treatment.

In conclusion, this study demonstrates a normalisation of height and improvement in body composition in children with a genetic diagnosis of PWS during the first 2 years of GH therapy, thus supporting the effectiveness of the current Australian GH programme. This was achieved without any serious adverse events reported to date. The improvement in body composition is encouraging and may possibly assist children with PWS to maintain a healthy weight, thereby reducing the risk of obesity-related complications in adulthood. Early referral to paediatric endocrinology is important so that GH treatment may be initiated and assist in early intervention before obesity or other complications affect eligibility.

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