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Benefit of Early Commencement of Growth Hormone Therapy in Children with Prader-Willi Syndrome

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ABSTRACT

Prader-Willi syndrome (PWS) is a chromosomal disorder and growth failure is a common presentation. Growth hormone (GH) treatment is beneficial in PWS although the optimal age for starting GH is unknown. We investigated whether GH response in PWS was associated with the age of GH commencement by comparing 16 children who commenced GH before 3 years of age (early group) with 40 children who commenced GH after 3 years of age (late group) from the Ozgrow database. Height SDS, body mass index (BMI) SDS, bone age (BA)-chronological age (CA) ratio, change in height (Δ Ht) SDS and change in BMI during 4 years of GH treatment were compared between the groups. The early group had better height SDS and Δ Ht SDS. BA delay was more pronounced in the early group but BA did not mature beyond CA with GH therapy in either group. Although the initial GH dose for the early group was lower than that of the late group, the former had better height outcome. The starting GH dose seen in the database is lower than the dose used by international centres.

KEY WORDS

Prader-Willi syndrome, PWS, growth hormone, GH, benefit, Ozgrow

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INTRODUCTION

Prader-Willi syndrome (PWS) is a genetic disorder characterised by growth failure, hypogonadotrophic hypogonadism, hypotonia, sleep-related breathing disorders, developmental delay, behavioural problems, hyperphagia and obesity[1]. It is due to loss of imprinted gene expression from the paternal chromosome 15q11-q13 region. Normally paternally inherited genes in this region are expressed while maternal genes are inactivated. Loss of expression most frequently occurs due to paternal deletion of this region (70% of PWS)[2,3] or less frequently due to maternal uniparental disomy of chromosome 15 (25% of PWS)[3-5]. The remaining 5% of PWS is caused by other structural abnormalities on chromosome 15, such as microdeletion within the PWS imprinting gene centre[3,6-8].

Patients with PWS have impaired growth hormone (GH) responsiveness during stimulation testing with GH releasing hormone and arginine[9], and numerous studies have described the benefits of GH therapy in this syndrome[10-16]. Children with PWS treated with GH (1 $mg/m^2/day$) for 2 years demonstrated normalisation of height standard deviation score (SDS), faster growth in head circumference, increased lean body mass accrual and decreased body fat together with improved language and cognitive functions[15]. In another study GH was continued for a total of 4 years in three cohorts receiving different doses of GH. The benefit on growth velocity, body composition (lean body mass) and resting energy expenditure was noted with higher doses of GH (7 $mg/m^2/wk$ and 10.5 $mg/m^2/wk$) but not with a dose of 2.1 $mg/m^2/wk$. Bone mineral density, however, improved in all studied doses of GH[12]. Moreover, GH improved sleep-related breathing disorders in children with PWS in a study in which 19 out of 25 patients showed improvement in the Apnoea/Hypopnoea

Index (AHI) and Central Index (CI), but not of the Obstructive Index (OI) when polysomnography 6 months after commencement of GH was compared to that of baseline[17].

However, in a mortality review in patients with PWS, the majority of sudden death was related to respiratory pathology[18,19] and this finding was also supported by a study of KIGS, the Pfizer International Growth Database[20].

Aim and hypothesis

Few published studies have investigated the optimal age for starting GH therapy in children with PWS. The aim of this study was to determine whether GH responsiveness was related to age at commencement of GH. Our hypothesis was that the earlier GH is started, the better the linear growth and body composition compared to starting GH therapy at older age. The biological rationale is that GH sufficient children under 3 years of age have greater height velocity. If children with PWS younger than 3 years of age receive GH early, this height velocity can be restored. Earlier commencement of GH may lead to better body composition because of earlier lean body mass accrual. It may in turn result in higher energy expenditure since lean tissues such as muscles have very active metabolism.

METHODS

We performed a retrospective analysis on growth data from the Ozgrow database of Australia and New Zealand regarding children with PWS on GH therapy. The Ozgrow database was established by the Australasian Paediatric Endocrine Group (APEG) in an attempt to collect data pertaining to GH therapy in children in Australia and New Zealand. GH therapy in Australia and New Zealand is subsidised by the federal governments and all applications for GH for various indications are captured and entered into the database.

The eligibility criteria for GH therapy according to the Department of Health and Aging of the Australian Government are short stature (height less than the first percentile as judged from the World Health Organisation International References for Growth which is based on data produced by the Centers of Disease Control, U.S. Department of Health and Human Services) and growth velocity less than the 25th percentile for bone age; or biochemical GH deficiency, that is peak GH level less than 10 mU/l in two challenge testings, plus a growth velocity less than the 25th percentile. There were no New Zealand patients included in this report.

The GH prescribers, who are paediatric endocrinologists or experienced general paediatricians, provide the diagnoses for short stature at the application for GH. The database records the diagnoses supplied by the GH prescribers as Ozgrow diagnostic codes. Growth data of children with the diagnostic code of 'Dysmorphic and Genetic Syndromes – Prader-Willi Syndrome' were extracted from the database.

The children with PWS who had GH treatment or are currently receiving GH were analysed. Those with no growth data for a minimum of 6 months or who did not qualify for GH therapy were excluded from the analysis. Sixteen patients (8 males and 8 females) who commenced GH before 3 years of age (early group [EG]) and 40 (24 males and 16 females) who commenced after 3 years of age (late group [LG]) were included in the study. Data up to 4 years after GH commencement were analysed.

The age- and sex-specific SDSs were calculated for height and body mass index (BMI) using the Centers for Disease Control 2000 reference data. Change in height SDS (Δ height SDS) after 1, 2, 3 and 4 years of GH therapy was calculated from baseline to assess the progressive nature of linear growth; and change in BMI SDS (Δ BMI SDS) was calculated for each year as a marker, albeit weak, for change in body composition[21,22]. The Ozgrow database records annual bone age assessment using the Greulich and Pyle method. The ratio of bone age to chronological age (BA:CA), which represents skeletal maturation in relation to chronological age, was calculated for each year.

Growth responsiveness was compared between EG and LG. The mean values of height SDS, BMI SDS, BA:CA, Δ height SDS, and Δ BMI SDS for each year up to 4 years of GH therapy were used in the comparison.

Statistical analysis

For statistical analysis, two sample t-test and Mann-Whitney U test were used for comparing means of the two groups; and linear regression for effect of age at commencement and height SDS at baseline on improvement of height SDS at the end of 4 years. All statistical procedures were performed using SPSS 15.

RESULTS

Baseline values of height SDS, BMI SDS, BA:CA and starting GH dose for the two groups are shown in Table 1. Prior to commencement of GH therapy, height SDS in the two groups was similar but BA:CA of the EG was less than that of LG, that is, the bone age delay was greater in the EG (p = 0.0006). The mean starting GH dose was

TABLE 1

Comparison of variables in the early group (EG) and late group (LG) before commencing GH therapy

	Early group n = 16	Late group n = 40	p
Male:Female	8:8	24:16	0.1260
Ht SDS before GH therapy	-2.68 (0.76)	-2.77 (0.75)	0.6700
BMI SDS before GH therapy	-0.25 (1.8)	+0.67 (1.77)	0.0900
BA:CA before GH therapy	0.53 (0.19)	0.75 (0.18)	0.0006
GH dose at commencement ($mg/m^2/wk$)	4.50 (0.97)	5.10 (1.14)	0.0700

Values of growth data and GH dose are shown as means (SD).

TABLE 2

Results of height SDS, BMI SDS and BA:CA [mean (SD)] with GH therapy in the early group (EG) and late group (LG)

	Height SDS			BMI SDS			BA:CA		
Group	**EG**	**LG**	**p**	**EG**	**LG**	**p**	**EG**	**LG**	**p**
1st year	-1.61 (0.67)	-2.17 (0.75)	**0.020**	-0.37 (0.83)	0.56 (1.72)	0.07	0.53 (0.22)	0.76 (0.15)	**0.0000**
n	16	40		13	39		12	38	
2nd year	-1.12 (0.66)	-1.91 (0.75)	**0.002**	-0.14 (1.18)	0.71 (1.76)	0.13	0.72 (0.20)	0.78 (0.21)	**0.0330**
n	15	33		12	32		12	30	
3rd year	-0.71 (0.66)	-1.68 (0.84)	**0.001**	0.23 (1.21)	1.16 (1.55)	0.07	0.71 (0.17)	0.86 (0.16)	**0.0023**
n	13	29		12	28		11	23	
4th year	-0.70 (0.59)	-1.54 (0.72)	**0.003**	0.73 (1.38)	1.41 (1.83)	0.31	0.82 (0.16)	0.89 (0.17)	**0.0484**
n	11	19		10	18		10	20	

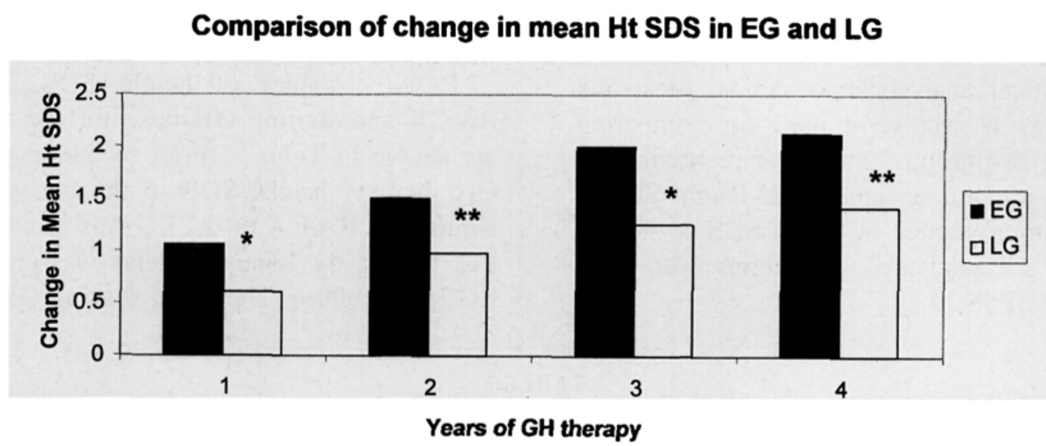

Fig. 1: Comparison of mean Δ height SDS with each year of GH therapy in the early group (EG) and late group (LG). *p = 0.001, ** p = 0.002.

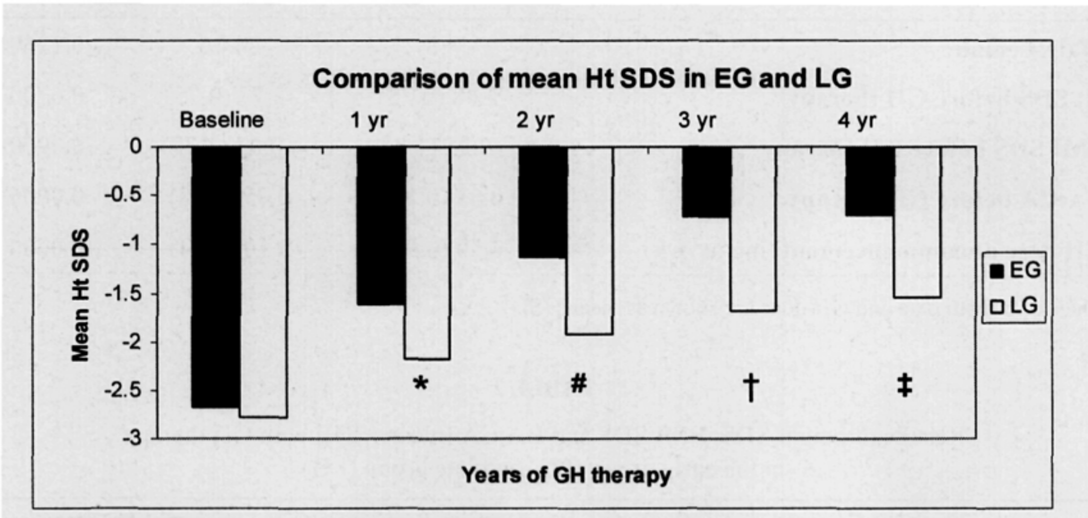

Fig. 2: Comparison of mean height SDS with each year of GH therapy in the early group (EG) and late group (LG). * p = 0.020, # p = 0.002, † p = 0.001, ‡ p = 0.003.

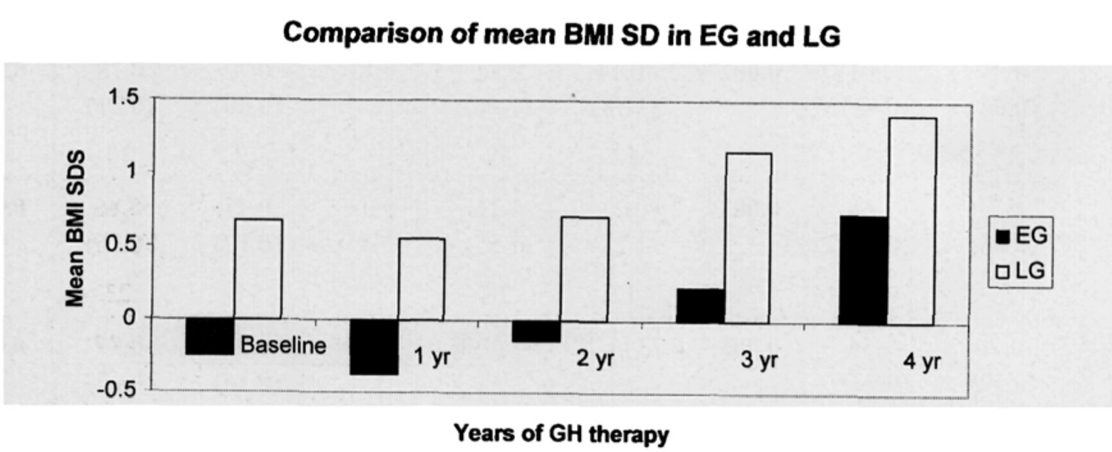

Fig. 3: Comparison of mean BMI SDS with each year of GH therapy in the early group (EG) and late group (LG).

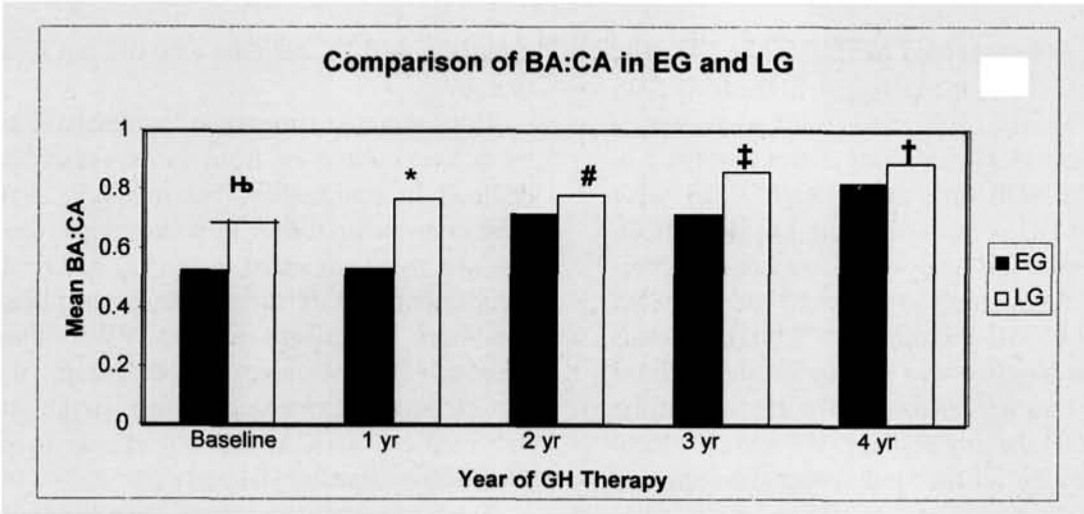

Fig. 4: Comparison of mean BA:CA with each year of GH therapy in the early group (EG) and late group (LG). [Hb] p = 0.0006, * p = 0.0000, # p = 0.0330, ‡ p = 0.0023, † p = 0.0484.

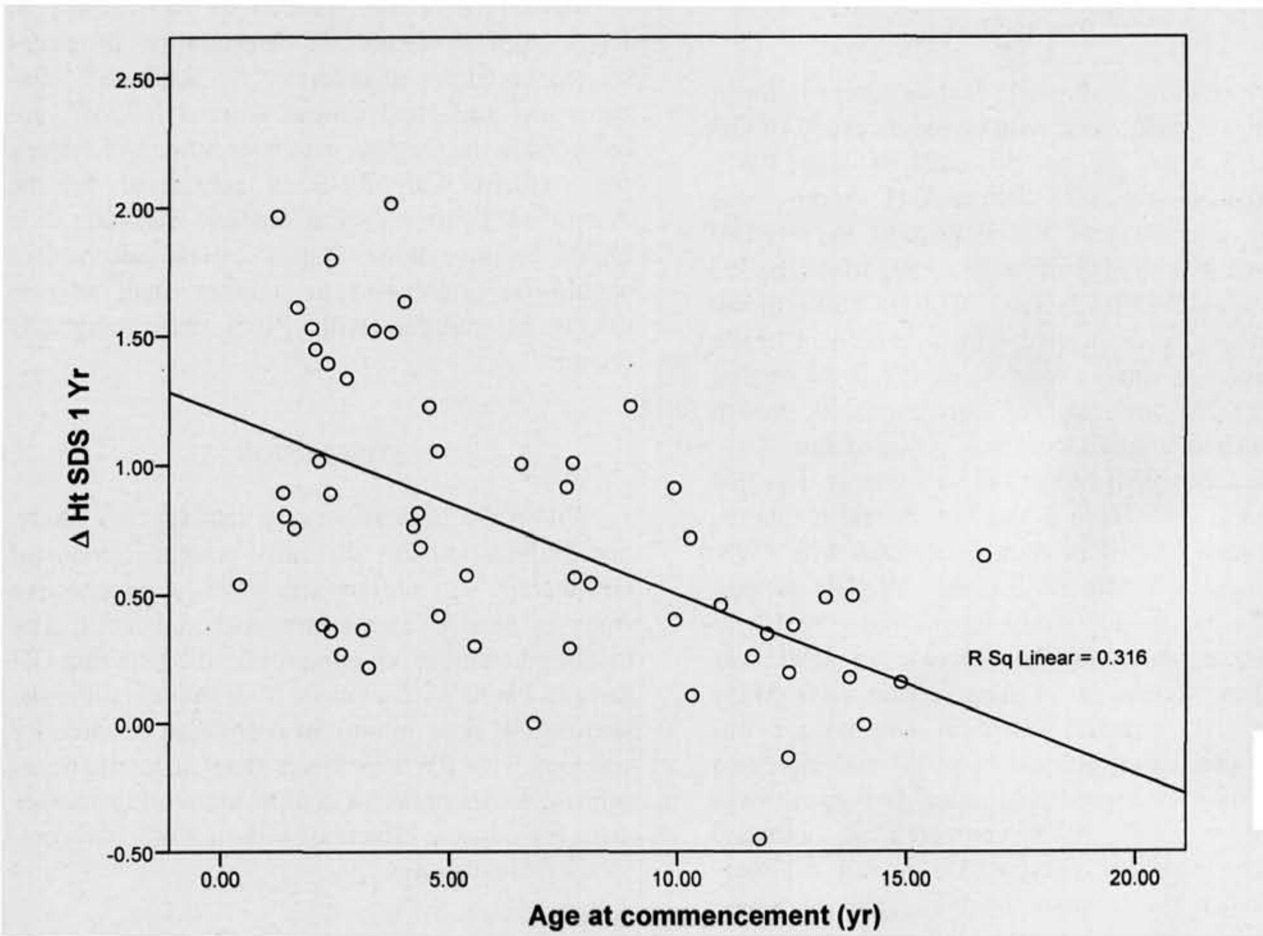

Fig. 5: Relationship between Δ height SDS at the first year of GH treatment and age of commencement.

lower in the EG compared to that of the LG. The mean Δ height SDS, mean height SDS, BMI SDS and BA:CA between EG and LG for each year of GH therapy are shown in Table 2 and Figures 1-4. The Δ height SDS and mean height SDS were greater in the EG compared to the LG (Figs. 1, 2, Table 2). Regression analysis showed age of commencement significantly influenced height SDS after 4 years of GH therapy ($p = 0.003$), whereas height SDS at baseline was not significantly related ($p = 0.178$). Linear regression of Δ Ht SDS at the first year of GH therapy and age of commencement of GH therapy for all the study population showed a negative relationship ($R^2 = -0.316$, $p < 0.0001$) (Fig. 5). BA delay was more pronounced in the EG and it did not mature beyond CA in either group (see Table 2 and Fig. 4). Δ BMI SD for 4 years of GH therapy did not reach statistical significance (Fig. 3).

DISCUSSION

Our findings showed that improved linear growth was associated with commencement of GH before 3 years of age in children with PWS. Although height SDS before GH therapy was similar, after 4 years of GH therapy, the EG had achieved height SDS of -0.70 (0.59) while the LG achieved -1.54 (0.72) ($p = 0.003$). This clinical benefit is also associated with a benefit in health economics as smaller total doses of GH for smaller surface area are required for improved growth outcomes in children less than 3 years of age.

The mean BMI of the LG was greater than that of the EG (see Table 2 and Fig. 3) and it may be due to poor feeding in younger children with PWS. BMI increased with time even with GH therapy (Fig. 3) but in this study it was not possible to differentiate whether the increase in BMI was related to increase in fat mass or lean mass. Many studies[11,13,23] reported that body composition improved (decreased percent body fat and increased lean body mass) with GH therapy (7-6 mg/m^2/wk) in children with PWS compared to untreated children. As body composition is not routinely recorded in the Ozgrow database, BMI SDS was used as an approximation. In our study, it was not possible to compare the BMI of our GH treated groups with PWS patients who did not receive GH therapy.

Bone age assessments in the database are made by different observers from various centres and it is difficult to standardize, but our BA:CA findings were consistently linear in both groups (see Fig. 4). BA was more advanced in the LG before the commencement of GH therapy and this phenomenon has been described in the PWS literature[24]. Although BA increased in both groups, it did not mature beyond chronological age. Height potential, indicated by BA:CA, did not appear to be compromised by starting GH early.

From our data it was found that the starting GH dose used in the PWS literature was greater than the current Australian practice[15,25]. It was not possible to extrapolate whether a higher starting dose in our cohort might result in better growth outcome or increased development of adverse effects.

No adverse effects related to GH therapy in PWS, such as death[20,26], deterioration of sleep-related breathing disorders[20,26,27], scoliosis[28], diabetes mellitus[20] and central adrenal failure[29], are recorded in the Ozgrow database. Since GH therapy for children with PWS is subsidised by the Australian Pharmaceutical Benefit Scheme, it is highly recommended that a central mechanism should be established to monitor such adverse effects in children with PWS undergoing GH therapy.

CONCLUSION

Within the limitations of a retrospective study, our findings support the early commencement of GH therapy in children with PWS. A prospective study is needed to confirm such a benefit. The height potential is not compromised by starting GH early in PWS. As is evident from the literature, the starting GH dose in current Australian practice for children with PWS is lower than in international centres. Furthermore, a central monitoring mechanism for adverse effects of GH in PWS is recommended in Australia.

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