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Diagnosis and treatment of GH deficiency in Prader–Willi syndrome

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Prader–Willi syndrome (PWS) results from under-expression of the paternally-derived chromosomal region 15q11-13. Growth failure is a recognized feature of PWS, and both quantitative and qualitative defects of the GH/IGF-I axis revealing GH deficiency (GHD) have been demonstrated in most children with PWS. In PWS adults, criteria for GHD are biochemically fulfilled in 8–38% of the studied cohorts. Published data support benefits of early institution of GH therapy (GHT) in PWS children, with positive effects on statural growth, body composition, metabolic homeostasis, and neurocognitive function. Like in pediatric PWS, GHT also yields beneficial effects on lean and body fat, exercise capacity, and quality of life of PWS adults. Although GHT has been generally administered safely in PWS children and adults, careful surveillance of risks is mandatory during prolonged GH replacement for all PWS individuals.

Introduction

Prader–Willi syndrome (PWS) is a complex disorder associated with multiple clinical manifestations resulting from the failure of expression of paternal alleles in the PWS region of chromosome 15 (15q11.2-q13). The principal genetic mechanisms responsible for PWS are deletion of the paternal

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chromosome 15 (del15) (type I or II, depending on the proximal breakpoint), maternal uniparental disomy for chromosome 15 (UPD15) or defects in the genomic imprinting center [1]. PWS affects both sexes and all races, with an estimated prevalence rate in the general population of 1:10,000–1:30,000 [2], reaching 10.7% among infants with hypotonia [3].

The syndrome shows a characteristic phenotype which encompasses neonatal hypotonia and failure to thrive, progressive hyperphagia with early childhood-onset obesity (if uncontrolled), developmental impairment with learning disabilities, behavioral and psychiatric issues, dysmorphic features, and endocrine abnormalities [2]. Altogether, the clinical picture of PWS seems to be related to a complex hypothalamic dysfunction [4].

Numerous endocrine disturbances have been associated with PWS including hypogonadism, central adrenal insufficiency and hypothyroidism [5]. Short stature is typical of the syndrome [2]. Up to 50% of infants with PWS are born small for gestational age (SGA) [6]. A peculiar pattern of growth is described, with significant decrease in growth velocity after age 2–3 years. At puberty, children with PWS fail to show growth acceleration and, without treatment, the final height is almost always lower than the mid-parental height. In order to assist the clinician in monitoring growth, standardized anthropometric curves for non-GH-treated infants and children with PWS have been generated [7,8].

GH secretory status

Multiple studies on PWS pinpointed the status of reduced GH response to various GH secretory stimuli, as well as inadequate spontaneous 24-h GH secretion [4]. In the observational KIGS database, GH deficiency (GHD) was found in three quarters of 424 children with PWS [9]. More than 80% of 113 children and 102 pre-pubertal individuals of a French PWS cohort fulfilled criteria for GHD after stimulation tests [10]. Due to the common occurrence of obesity, however, it has been argued that reduced GH secretory pattern in children and adolescents with PWS may reflect excessive fat body mass. In this light, a higher prevalence of GHD has been found in obese PWS children in comparison to non-obese PWS subjects [11]. The PWS phenotype, however, resembles the classical syndrome associated with GHD due to diseases other than PWS. Apart from short stature, both children with PWS and GHD have increased body fat, decreased lean body mass, reduced muscle strength, impaired bone mineral density and psychological impairment [2,4]. Inversely, young subjects with simple obesity maintain adequate or enhanced linear growth velocity and tend to have an increased absolute fat free mass. A true GH/IGF-I axis dysfunction in children and adolescents with PWS is confirmed by the finding of a high prevalence of GHD (i.e., 87%) also in non-obese PWS subjects [12].

Biochemical GHD has been found to be less prevalent at ages up to 18 months (27%) compared with older children (81%), suggesting that pituitary GH reserve gradually declines in pediatric cohorts with increasing age and body mass index (BMI) [11]. According to the hypothesis that GHD in PWS may reflect an evolving process, very young PWS children seem to have impaired hypothalamic GH-Releasing Hormone (GHRH) secretion with a normal GH pituitary reserve [13]. However, further studies are needed to confirm the hypothesis of an age-related decline of GH secretion.

Genetic subtypes seem to influence the response to the stimulation tests, with a higher incidence of GHD in UPD15 subjects than patients with del15 [13–15]. Moreover, qualitative evaluation of GH responsiveness to GHRH + arginine by deconvolution analysis highlighted the most delayed GH response in UPD15 children compared to del15 PWS subjects [16].

In consequence of such altered GH secretory pattern, and opposed to what occurs in simple obesity, most PWS children harbour decreased IGF-I levels, which are not related to BMI [4,17].

In summary, the combination of reduced GH and IGF-I levels indicates that, as a group, pediatric individuals with PWS are GHD. Consequently, current guidelines suggest that GH testing is not required before GH therapy in affected infants and children (Table 1) [17,18].

In the adult stage, determining the presence of GHD after attainment of final height may be beneficial, because reports from dynamic testing in adults suggest that GHD is not universal in PWS (Table 1) [17]. When diagnosis of GHD was tested by insulin or arginine tests and peak GH levels <3 mcg/L were used, biochemical criteria of GHD were fulfilled by 40–67% of cases [23,24]. Alternatively, when GH response was tested by GHRH + arginine and cut-off values of <16.5 mcg/1

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Table 1
Current indications for diagnosis of GH deficiency in Prader–Willi syndrome [adapted from Grugni et al. [19]].

Age	GH provocation tests	Peak GH cut-off level for diagnosis of GHD	References
Childhood	Not requested		Deal et al. [17] Goldstone et al. [18]
Transition phase	GHRH + arginine	<19 μg/L[a]	Corneli et al. [20]
	Insulin tolerance test	<5 μg/L	Clayton et al. [21]
Adulthood	GHRH + arginine	BMI < 25: <11.5 μg/L; 25 < BMI < 30: <8 μg/L; BMI > 30: <4.2 μg/L	Corneli et al. [22]
	Insulin tolerance test	<3 μg/L	Clayton et al. [21]

[a] Italian criteria for determining GHD in PWS during transition phase: (i) three or more pituitary hormone deficiencies; (ii) a peak GH level after GHRH-arginine test <4.1 μg/L after a GH wash out period prior to retesting of at least 1 month. For abbreviation: GHD, GH deficiency; GHRH: GH-releasing hormone.

and < 9 mcg/l were used, criteria for GHD were fulfilled by 75% and 50% of PWS patients, respectively [24]. However, if the GH response to the GHRH + arginine test was based on BMI-related cut-off value to adjust for the severely obese phenotype of most PWS adults, GHD could be biochemically confirmed in 8–38% in adult cohorts [25–27]. Noticeably, GH response to GHRH + arginine in PWS adults is quantitatively and qualitatively affected when plotted against either BMI-matched controls or PWS children: by deconvolution analysis, GH response is lower, less robust and more delayed in the formers compared to the latters [16,28]. Like in pediatric PWS, the genuineness of GHD in adult PWS can be confirmed by markers of the somatotroph axis such as IGF-I. While in simple obesity hyposomatropinemia coexists with normal-to-high IGF-I values, IGF-I levels are usually below the age-adjusted values in PWS adults, indicating a true state of GHD [26,29], while IGFBP-3 do not appear to differ from normal [25]. At this stage, neither IGF-I nor IGFBP-3 correlate with BMI [25].

GH therapy

Published data currently support the beneficial effects of early institution of GH therapy (GHT) in children with PWS, thus recommending to start therapy between 4 and 6 months of age [17,18]. The standard replacement GH dosage is around 1 mg/m^2/daily or ~0.035 mg/kg/daily, achieved within approximately 1 month of commencing treatment at a lower dose and depending on individual tolerability. The objective of GHT is to reach a significant increase of IGF-I levels without exceeding the upper limits of the normal range [0 to 2 standard deviation score (SDS)], in order to avoid potential adverse effects due to overtreatment. However, it has been recently demonstrated that immunoreactive IGF-I values may not correlate with IGF bioactivity during GHT, thus questioning the ability of circulating IGF-I concentrations to appropriately reflect GHT dosing in PWS children [30].

In adults with PWS, the starting dose of GH currently recommended is 0.1–0.2 mg/daily, depending on age, previous GH exposure, presence of lower extremity edema and concomitant sex steroids use, especially in females [17]. Similarly to the pediatric age, subsequent dosage should be guided by maintenance of physiological levels of IGF-I, as well as by clinical response.

GHT and growth

The positive action of GHT on linear growth of PWS children is well established. Long-term GHT through childhood allows to restore final adult height, and is associated with the complete normalization of head circumference [31–33]. Scoliosis is not a contraindication to GHT [17]. Standardized growth curves for GH-treated PWS individuals aged 0–18 years have been recently developed [34]. The use of PWS-specific growth standards is strongly encouraged, in order to guide GHT through an appropriate monitoring of the growth rate. Baseline hand, foot, tibia length SDS and arm span SDS are significantly increased by GHT, though these indices remained significantly below 0 SDS in PWS children followed for 4 years during GHT [35].

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GHT effects on body composition and metabolic homeostasis

As already mentioned, early life stages of PWS are associated with failure to thrive and progressive loss of lean mass [36]. Starting from the age of 2.1–4.5 years, weight increases and PWS children tend to develop overt obesity [37] unless strict dietary control is followed. In PWS infants, the proportion of body fat increases compared to muscle mass even prior to the development of obesity [38]. In children aged 3–7 years, it has been reported that percent fat mass is 2.3 SDS higher and lean mass is 2.5 SDS lower than the reference age-matched population, indicating an unfavorable body composition [33]. Early institution of GHT during PWS childhood can significantly increase lean mass toward the normal range and delay fat tissue accumulation [36]. The response of body composition to GHT is prompt and remains unmodified if GHT is continued. Long-term data showed that lean body mass increased during the first year of GHT and remained stable thereafter at levels above baseline, while percent fat and BMI significantly decreased in the first year of GHT and remained stable at level not significantly higher than baseline [33]. Replacement GH dosing exerts a crucial role, considering that lower doses of GH do not appear to sustain effectively the improvement of body composition in children with PWS [35,39].

After childhood, the disease promotes further accumulation of subcutaneous (SAT) and visceral abdominal fat (VAT) along with advancing age and increasing BMI, while lean mass remains unmodified [40–42]. Obesity of PWS adults is phenotypically distinguished from simple obesity by predominance of fat mass over lean mass [42], lower trunk-to-appendicular fat mass ratio, and lower visceral adiposity [43,44]. Also, SAT adipocytes are larger and show lower expression of genes related to fibrosis and metabolic derangement compared to simple obesity, possibly denoting an ability of adipose tissue to expand with relatively milder metabolic burden [45]. In line with this reasoning, dyslipidaemia is generally infrequent, insulin levels and insulin resistance are usually lower, and features of the metabolic syndrome and liver steatosis are reportedly milder in PWS than obese controls [44,46–49]. The overall risk of glucose abnormalities is less marked than in BMI-matched controls, yet it worsens with aging and weight accrual. A multicenter study on 274 PWS patients of all ages showed abnormal glucose metabolism in 24.4% of subjects (Fig. 1) [50].

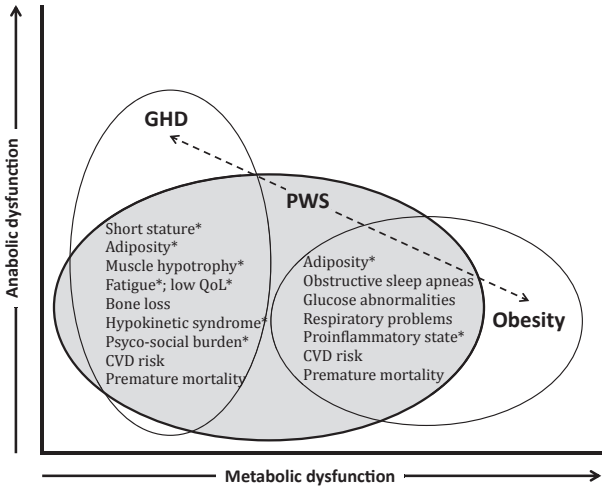

Fig. 1. Shared clinical domains between PWS, GHD and obesity. PWS and GHD share clinical domains related to anabolic and partly metabolic effects of the GH/IGF-I axis. PWS and obesity share clinical domains related to metabolic homeostasis and cardiopulmonary health. This setting proposes a multidimensional relationship between the typical PWS traits (described in the text) and anabolic-metabolic burdens of GHD and obesity. Items shown to improve with GHT in PWS populations have been indicated by an asterisk. For abbreviation: GHD, GH deficiency; QoL, quality of life; CVD, cardiovascular disease.

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It has been widely demonstrated that GHT yields beneficial effects on body composition of PWS adults, leading to increased lean body mass, decreased total body fat, as well as reduced SAT and VAT. Like in pediatric PWS, anabolic effects of GHT occur in the first year and remain unaltered thereafter unless GHT is withdrawn. Changes are quantitatively modest but sufficient to improve muscle utilization, fatigue and self-rule, thus helping to control the course of the disease [51–54]. Intuitively, this supports the need for continuation of treatment also during transition from childhood to adulthood, and possibly in PWS adults previously untreated during childhood [33,52,55]. GHT only marginally impacts resting metabolic rate [52], while it slightly increases body water content [27]. Long-term GHT does not seem to influence glucose homeostasis at any age [33,56], although a slight increase in glucose levels and insulin resistance has been observed in a meta-analysis [53]. Hypothetically, impaired glucose metabolism during GHT could mainly result from weight gain rather than GHT [56]. To avoid the potential diabetes risks associated with GHT, PWS with severe obesity and uncontrolled diabetes mellitus should be excluded [17].

Lipids improvements in PWS are modest during GHT, likely due to the low prevalence of dyslipidaemia and the relatively low visceral adiposity if compared to simple obesity or GHD [53].

GHT, neurocognitive function and quality of life

Emerging data in children with PWS showed beneficial effects of GHT on psychomotor development, with significant improvement in abstract verbal reasoning and visuospatial skills [57]. GHT was shown to be effective in increasing vitality and behavioral issues, while its withdrawal led to a marked deterioration of behavioral problems [58]. Improvement in health-related quality of life during long-term GHT was also observed, in comparison to untreated children [59]. It is of note, however, that GHT seems to be unable to normalize cognitive abilities of PWS children, although may reduce the disparity in mental development compared with non-PWS individuals [60].

With regards to PWS adults, it has been previously reported that GH availability and higher IGF-I levels may have favorable effects on cognitive function and emotional aspects [61,62]. PWS adults showed improvement in quality of life and feelings of well-being during GHT, such as mental speed and flexibility [63]. Conversely, the presence of active psychosis is a contraindication to GHT both in children and in adults with PWS [17].

GHT and bone

Bone characteristics seem to differ between children and adults with PWS, with children showing a normal bone mineral density (BMD), when adjusted for their short stature [64,65]. During the transition phase and adulthood, PWS subjects have reduced total BMD and BMC. As a result, an increased frequency of fractures and osteoporosis is observed. The causes for this bone fragility have been linked to a complex interaction of different factors, including endocrine abnormalities, low neuromuscular activity, and reduced calcium intake and vitamin D levels [66]. Animal data suggest that deletion of the imprinted Prader–Willi critical region, including the Snord116 cluster, may play a role in bone homeostasis [67].

Long-term data on GHT in PWS children show that BMD remains stable in pre-pubertal patients but it tends to decrease in adolescence [68], while in adults bone mass is not improved by GHT given for 2 years [69]. Together, these results suggest that bone impairment is not exclusively driven by GHD in PWS. Data on GHT and BMD in PWS, however, are not univocal, and other studies have demonstrated that GHT exerts a beneficial effect on bone mineralization and bone geometry in PWS patients [70,71]. The reason for this discrepancy remains to be clarified, but it may be related to the wide range of factors involved in determining or maintaining low bone mass, such as body weight status, lifestyle factors, and appropriate management of the endocrine issues in PWS patients, including duration of GHT and concomitant sex hormone replacement at appropriate age [6,17,18].

GHT and muscle

GHT exerts a positive effect on skeletal muscle characteristics and motor performance, affecting the natural history of PWS in a beneficial way. After 2 years of GHT, the muscle ultrasound scans show a

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significant increase of muscle thickness in infants with PWS, which is highly correlated to muscle strength and motor development [72]. Improvement of muscular functioning during GHT is maintained over the years, particularly if treatment is started early in life [73], and if patients are actively involved in a training program [74]. Decreased motor performance is a major source of concern in PWS during adulthood. In this context, exercise intensity was found to be improved by 16% after 6 months and by 19% after 12 months of GHT in adult subjects with PWS [75]. In these patients, long-term GHT has been proven to be effective in increasing muscle size and quality, muscle strength, and exercise tolerance [54]. Amelioration of motor performance tests during GHT has been found in another group of 19 PWS adults, with a rapid deterioration in motor skills after GHT withdrawal [62]. It is noteworthy that GHT leads to a significant improvement of muscle strength and exercise capacity in PWS adults both with and without biochemical GHD [54,75].

Respiratory function

PWS patients are affected by abnormalities of sleep breathing and wakefulness, disturbances in the organization of sleep, restrictive lung disease and alveolar hypoventilation, all of which result in nocturnal hypoventilation with oxygen desaturation, sleep apnea, abnormal arousal response during hypercapnia leading to excessive daytime sleepiness [76,77]. These disorders have been related to cases of sudden death in PWS infants [78]. In non-obese prepubertal PWS children, central sleep apneas are more frequent than obstructive sleep apneas (OSAs) and seem to imply a primary central defect of the respiratory control [79]. Alterations in sleep architecture that may reflect central dysfunctions have also been described [80,81]. During their lifetime, PWS patients become prone to suffer predominantly from OSAs. This likely reflects the underlying progression of obesity, but may be also be exacerbated by nasopharyngeal dysmorphisms and muscle hypotonia [82]. While the actual prevalence of OSAs remains debated, PWS adults show more severe apnea-hypopnea indices, lower oxygen saturation, and higher rate of oxygen desaturation <90% if compared to simply obese counterparts [47]. A case-control study found polysomnography criteria for OSAs and severe OSAs in 95% and 21% of obese PWS patients, respectively, while 47% showed signs of obesity hypoventilation syndrome [83].

Treatment of breathing disorders in PWS does not differ from that of normal children or adults. OSAs benefit from successful management of obesity, use of non-invasive or (when necessary) invasive nocturnal ventilation and, occasionally, from surgical approach in case of anatomical constraint due to adenotonsillar hypertrophy. In pediatric PWS, OSAs have gained increasing attention due to the potential effect of GHT on adenotonsillar enlargement and sudden death. From 2002 to 2005, several cases of fatal events during the first months of GHT have been reported, being respiratory involvement the most common cause of deaths [84]. In this respect, current data seem to exclude a cause–effect relationship between mortality and GHT [5,85], but the question remains open [86]. A recent 48-month follow-up study in PWS children confirmed that on average GHT does not impair sleep breathing, while advising caution to avoid potential development or worsening of OSAs, particularly within the first months of GHT initiation [87]. In order to safely administer GHT in the long-term, children and adolescents with PWS should undergo a multidisciplinary evaluation before starting and during the treatment, including polysomnography, ear, nose and throat (ENT) evaluation. The observation of adenotonsillar hypertrophy during GHT suggests ENT surgery. As a precaution against sleep-related breathing disorders, GHT should be suspended during subsequent episodes of acute respiratory infection [17]. In adults with PWS, GHT has been associated with an improved peak expiratory flow by 12%, which is suggestive of increased muscle strength or improved muscle function [27]. After short-term GHT, however, 10% of adults with PWS had worsening of sleep disturbance [86]. Thus, a complete clinical and instrumental assessment is mandatory before and during GHT.

GHT and heart

Beyond occasional reports on congenital cardiac defects in PWS infants [88], current data are inadequate to support the hypothesis that PWS predisposes to clinically overt cardiovascular

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malfunctions. During their lifespan, however, both PWS adolescents and adults are exposed to a high risk of sudden death suspected to be cardiopulmonary in origin, even in the absence of predisposing factors beyond obesity [85,89–92]. Subtle alterations have been occasionally documented in PWS children by ECG (high voltages in precordial leads, first-degree atrioventricular block, pathological Q wave, and prolonged QT interval), echocardiography (atrial septum defect, pulmonary valve stenosis) and 2D speckle tracking echocardiography (lower peak systolic strain values) [93]. After 1 year of GHT, one study reported a significant improvement of diastolic filling, while documenting a near-significant reduction of shortening fraction, a systolic index [94].

In adults with PWS, there is evidence of occasional ECG abnormalities during ergometry with one case of sporadic sinus arrest requiring pacemaker insertion [95]. Microvascular responses to ischemic stress are significantly impaired in PWS patients, while carotid intima media thickness is non-significantly greater in patients with PWS compared with controls [95]. Echocardiography studies generally showed no clinically meaningful abnormalities [47,95]. In a case-control study, subtle structural and functional alterations of the left ventricle, such as lower values of cardiac mass and diastolic filling, were seen when compared with obese controls, while cardioscintigraphic study documented a lower chronotropic and inotropic response of the left ventricle during adrenergic stimulation with dobutamine compared with BMI-matched controls [47]. Data on long-term GHT documented that 4 years of GH administration can contribute to stabilize cardiovascular structure of PWS adults, although the presence of subtle modifications in systolic and diastolic function suggests the need to monitor heart function during therapeutic management of PWS [55]. It is finally important to note that PWS obesity may impair precise echocardiography assessment.

Summary

The combination of reduced GH and IGF-I levels indicates that, as a group, pediatric individuals with PWS suffer from GHD. The multifold benefits of GHT for PWS children are well established, with satisfactory effects on linear growth, body composition, physical function, cognitive development, and metabolic parameters. A minority of adolescents and adults with PWS met criteria for severe GHD. However, GH secretion is impaired in PWS adults both as amplitude, such as the peak value, and as quality of pituitary response, such as the shape of the secretory profile. During adulthood, available data demonstrate a positive effect of GHT on lean mass, skeletal muscle characteristics and motor performance, peak expiratory flow, metabolic health, and psychological well-being. Consequently, testing for the GH secretory pattern may be beneficial in all PWS patients at near adult height.

After more than 15 years of clinical experience, GHT shows a reasonably good safety record. To avoid potential risks, at all ages the goal of substitutive therapy is to achieve hormone replacement with normal serum IGF-I levels. In PWS patients with severe obesity, clinically overt glycemic alterations and uncontrolled respiratory impairment should advise against starting GHT.

Practice points

- GH testing is not required before starting GHT in affected infants and children;
- Testing for GHD should be performed in all PWS patients after achievement of final height in the absence of contraindications, and BMI-related cut-off points for GH stimulation tests should be used if the GHRH + arginine test is used (Table 1);
- GHT dosing should be guided by maintaining IGF-I within physiological levels (0 to +2 SDS);
- The goals of GHT are to increase final height in children, and at all ages to ameliorate body composition, physical strength and agility, psychological aspects and metabolic markers;
- Because of the paucity of data, long-term surveillance of benefits and risks of GHT is strongly recommended for the whole PWS population.

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Research agenda

- To evaluate the importance of GH secretory status (GHD versus non-GHD) on GHT effects;
- To analyze the effects of GHT in children born small for gestational age in comparison to subjects born appropriate for gestational age;
- To assess the GH secretory response and the clinical effects of GHT during aging;
- To profile the role of gender and genotype with respect to the clinical response to GHT;
- To detail the relationship between GHT and bone health;
- To establish how concomitant therapies (sex hormones, vitamin D, etc.) and lifestyle factors (nutrients intake, motor activity, etc.) impact on GHT efficacy;
- To assess the impact of long-term GHT on morbility and premature mortality of PWS;
- To thoroughly evaluate the cardiovascular and respiratory effects of long-term GHT.

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