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Is There Growth Hormone Deficiency in Prader-Willi Syndrome?

Six Arguments to Support the Presence of Hypothalamic Growth Hormone Deficiency in Prader-Willi Syndrome

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Key Words

Prader-Willi syndrome · Prader-Labhart-Willi syndrome · Growth hormone therapy · Growth · Syndromal obesity · Body composition · Lean body mass · Fat mass · Hand length · Foot length

Abstract

Prader-Labhart-Willi syndrome (PWS) is the most frequent form of syndromal obesity. Its main features are associated with hypothalamic dysfunction, which has not yet been comprehensively described. The aim of this review is to present arguments to define the presence of genuine growth hormone (GH) deficiency (GHD) in these patients. Decreasing growth velocity despite the onset of obesity, reduced lean body mass in the presence of adiposity, small hands and feet, relatively low insulin-like growth factor-I and low insulin levels, as well as the dramatic effect of GH treatment on growth, support the presence of hypothalamic GHD in PWS. Even though it might be difficult to ultimately prove GHD in PWS because of the obesity-induced counterregulation, the hormonal situation differs from that in simple obesity. The effects of long-term therapies with GH on body composition in these patients are summarized. GH therapy dramatically changes the phenotype of PWS in childhood: height and weight become normal and there is a sustained impact on the net loss of body fat. We conclude that GHD may account for several features of PWS.

Introduction and Scientific Background

Prader-Labhart-Willi syndrome (PWS) was first described in 1956 [1] and is the most common syndromal cause of marked obesity. Its incidence is estimated to be 1 in 16,000 live births [2]. PWS is caused by the absence of a specific part of the paternal homologue of the long arm of chromosome 15 due to a deletion [3] or to maternal uniparental disomy [4, 5]. The characteristic features during infancy are general muscle hypotonia, feeding difficulties and underweight due to poor sucking and swallowing reflexes. Between the second and fourth year of life, obesity sets in as a consequence of uncontrolled compulsive eating. PWS patients have characteristic facial features comprising a narrow bifrontal diameter, almond-shaped eyes, strabismus and a triangular mouth. Hypogenitalism and cryptorchidism are common features, accompanied by delayed psychomotor development, mental retardation and behavioural problems. Growth is characterised by moderate intrauterine and postnatal growth delay, lack of pubertal growth spurt and short stature as an adult: a male adult grows to an average of 152–162 cm, a female to an average of 145–150 cm [6, 7].

The link between the chromosomal disorder and the clinical manifestations is unknown. It is assumed that there is a dysfunction of several hypothalamic centres, but gonadotropin deficiency is the only clearly documented endocrine hypothalamic disorder [8]. However, there is growing evidence that growth hormone (GH) deficiency

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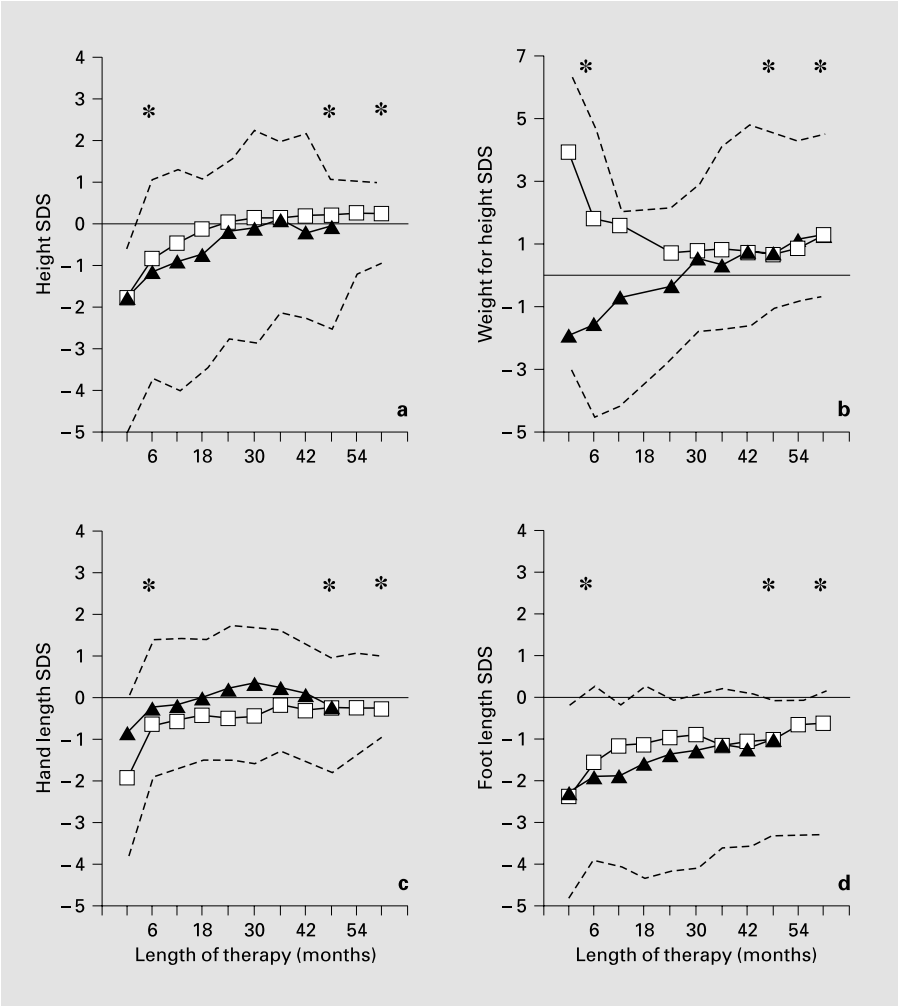

Fig. 1. Height SDS (**a**), weight for height SDS (**b**), hand length SDS (**c**) and foot length SDS (**d**) of children with PWS, referring to normative data of the Zürich Longitudinal Study [21], before and during up to 5.5 years of GH therapy. Values are shown for young, initially underweight children (▲, n = 10) and overweight prepubertal children (□, n = 8). Medians are shown as solid lines; minimum and maximum values of the combined group are shown as broken lines. Significant differences, tested at 6, 48 and 60 months by the Wilcoxon test, in each group vs. the value before therapy, are indicated as *$p < 0.05$.

(GHD) due to hypothalamic dysregulation may contribute not only to the abnormal growth pattern, but also to the excess of body fat [9] and the deficit of lean body mass (LBM) with consequent reduced energy expenditure [10].

In PWS the GH response to insulin, arginine, clonidine and dopa is reported to be low-normal or blunted [9, 11–15], as are sleep-induced GH secretion [16] and 24-hour integrated GH concentrations [12]. However, simple obesity is also associated with a decreased circulating concentration of GH, and spontaneous 24-hour GH secretion has been shown to be low and similar in both PWS and healthy obese controls [17]. There is evidence, however, that GH secretion in simple obesity is not disturbed, but downregulated and fully reversible by weight loss. Therefore, controversy has arisen as to whether the insufficient GH secretion in PWS is the consequence of obesity [18] or whether it represents genuine GHD due to hypothalamic dysfunction.

In order to search for arguments to support the presence of GHD in PWS, the present article compares the clinical and biochemical aspects of PWS with non-syndromal obesity and GHD without PWS.

Argument 1: Children with PWS Are Short in Contrast to Children with Non-Syndromal Obesity

Comparison of the dynamics of spontaneous growth in healthy obese children and in children with PWS supports the first argument in favour of GHD. Healthy obese children are taller than normal-weight children. During the prepubertal period after the age of 4, it has been shown that growth velocity is normal and bone age is already accelerated by up to 2 years [19]; therefore, acceleration of bone age and growth velocity must occur during the first

years of life. It is assumed that this acceleration is the consequence of high insulin secretion, which is correlated with the height standard deviation score (SDS) [19], and/or adrenal androgens, but the mechanisms are not yet entirely clear. However, during puberty in non-syndromal obesity, growth slows down, the pubertal growth spurt is smoothed, and adult height is within the normal range [19, 20].

Contrary to this picture, children with PWS are short for age (fig. 1a), despite their obesity, and their bone age is slightly retarded or normal. The spontaneous growth of 315 patients with PWS has recently been analysed [7]: at birth, the height and, even more so, the weight of babies with PWS are below the normal average. While during the first year, these children's growth is nearly normal, short stature becomes increasingly apparent thereafter. Between 3 and 13 years of age, the 50th percentile for height in PWS roughly equals the third percentile in healthy controls. This means that growth in children with PWS slows down while they become obese, in contrast with healthy obese children. On the other hand, when children with PWS enter puberty, their height is not as low and their bone age is less retarded than in children with isolated GHD. This may be attributed to the consequence of obesity and its related growth acceleration. Furthermore, adult short stature in PWS is in part the consequence of the lack of pubertal growth spurt [6, 7]. However, in contrast with hypogonadism [22], in PWS bone maturation does not slow down when pubertal bone age is achieved [7]. Instead, a lack of pubertal growth spurt combined with a normal progression of bone maturation is typical for isolated GHD without substitution, in the presence of normal pubertal sex steroid levels [22]. Thus we attribute the absence of the pubertal growth spurt to GHD rather than to partial hypogonadism.

In conclusion, the growth pattern in PWS considerably differs from that seen in non-syndromal obesity, bearing greater similarity to growth in GHD if some modification by overweight is taken into account.

Argument 2: Hands and Feet Are Short in PWS as in GHD

The second argument for GHD in PWS is the short hands and feet (fig. 1c and d) that are considered a typical sign of PWS. In 1991, Butler et al. [23] measured the reduced size of hands and feet in 57 PWS patients (–1.73 and –2.73 SD, respectively) in comparison with US reference values. We found similar results [24], namely a hand length of –1.5 SD and a foot length of –2.2 SD, using the Oosterwolde study as a reference [25]. Small hands and feet for reduced height are found in type-A GHD [26] and in Laron syndrome [27], both being extreme forms of GHD or GH resistance.

Argument 3: LBM Is Decreased in Both PWS and GHD in Contrast to Non-Syndromal Obesity

In healthy obese children, LBM is increased proportionately to fat mass [28]. However, it has been demonstrated that, in contrast to non-syndromal obesity, PWS children have not only increased fat mass but also decreased LBM.

By analysing the body composition of 27 PWS patients aged 6–22 years using dual-energy X-ray absorptiometry (DEXA) it was shown that LBM was significantly lower in PWS patients than in healthy age- and sex-matched controls with normal weight or, even more so, obesity (26.4 vs. 32.9 or 40.3 kg LBM, respectively) [29]. Yet relative body fat was significantly greater in PWS patients (47.4%) than in normal-weight (20.6%) or even in obese (41.9%) controls. Carrel et al. [30] also reported a low LBM in 54 PWS patients aged 4–16 years, LBM only accounting for about 55% of total body weight, whereas 80% is considered to be a normal relative LBM in healthy children [31]. Another method yielded similar results: van Mil et al. [32] calculated fat-free and fat mass, measuring total body water by deuterium dilution in 17 PWS patients aged 7–19 years, and showed that PWS patients had a lower fat-free mass in relation to fat mass than obese controls matched for gender and bone age. They concluded that PWS patients can store fat with a smaller fat-free mass gain, possibly related to disturbed endocrine status.

We measured body composition by DEXA in 16 PWS children (age 1.5–14.6 years) [33] and compared the results with reference data of healthy Caucasian US children [34, 35]. Since children with PWS are short for age before GH therapy, relating LBM exclusively to age could result in an underestimation. For this reason, LBM was adjusted for height in addition to age and gender. In overweight prepubertal PWS children above 5 years of age (median of weight-for-height 4 SD), LBM was reduced (median –1.8 SD) compared with healthy US reference values. The percentage of body fat was distinctly elevated in the overweight children and adolescents with PWS (medians 43 and 52%). Compared with reference values for Dutch children [36], the deficit of LBM in prepubertal overweight children with PWS and the excess of fat were even more evident (fig. 2). Even in young, still under-

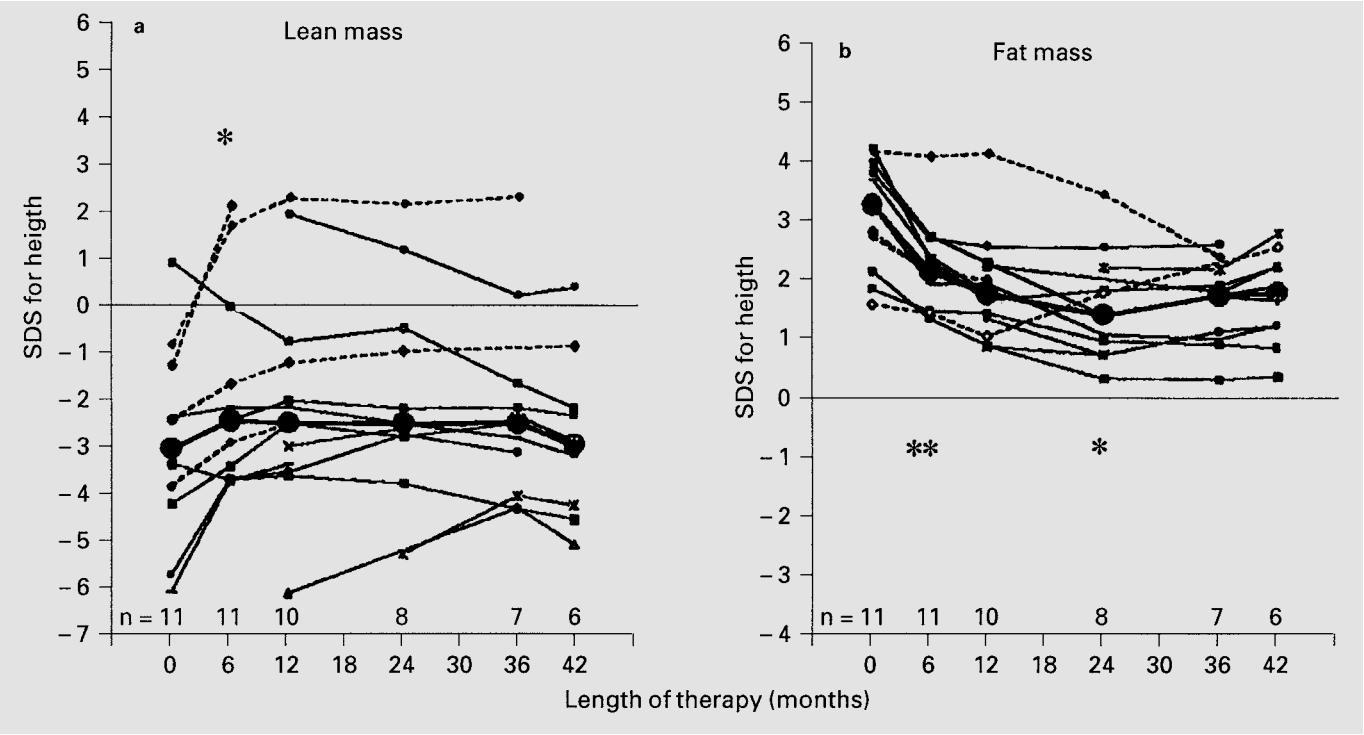

Fig. 2. Body composition measured by DEXA in 16 PWS children, expressed as height-related SDS of a Dutch reference population [36] in those taller than 100 cm; medians (●, solid lines) and individual courses of young underweight (n = 4, fine lines), prepubertal overweight (n = 8, circles and squares, fine lines) and pubertal PWS children (n = 4, ◆, dotted lines). Significant differences vs. baseline are calculated as indicated in figure 1: *$p < 0.05$; **$p < 0.01$.

weight children, subcutaneous fat was increased despite their low weight (compare fig. 1b), suggesting a reduction in LBM, as shown in a previous study [37]. Yet, it has also been shown in patients with GHD prior to GH substitution that body mass index (BMI) and body weight may still remain in the normal range despite altered body composition [38–40].

These data show that body composition abnormalities in PWS differ from those of simple obesity, resembling those of individuals with GHD. Several studies in children [38, 41], as well as in adults [42, 43], have demonstrated that in GHD LBM is reduced and fat mass is increased.

Argument 4: IGF-I Is Lower in PWS than in Non-Syndromal Obesity

It is well established that insulin-like growth factor (IGF)-I is low in children with GHD [44, 45]. In healthy obese children and adolescents, IGF-I is normal or elevated despite decreased GH secretion, but the reported results are inconsistent: while in recent studies, predominantly in prepubertal children, normal levels of IGF-I compared with lean controls have been found [46–48], in earlier studies [18, 49, 50] IGF-I was found to be raised, e.g. in pubertal or very obese children [51, 52]. Finally, there is growing evidence that free IGF-I, i.e. IGF bioavailability, is increased in obesity [46, 48, 53].

In PWS, IGF-I has been reported to be low (–1.46 SD) [9, 12] or in the low-normal range (0.52 U/ml, normal 0.4–4.5) [13]. In a recent study, Angulo et al. [54] described that of 44 children with PWS, 31 had IGF-I levels 2.5 SD below the mean for their age. In two further studies in PWS, including 29 children aged 3–12 years and 19 children aged 0.5–14.6 years, IGF-I levels were lower than those of obese control children (–1.5 SD and –0.2 SD, respectively, $p < 0.05$) [17] or those of healthy normal-weight references (–0.7 SD, $p = 0.002$) [55]. These findings support the assumption that GH secretion in PWS is insufficient to promote normal levels of circulating IGF-I.

The decreased IGF-I levels in PWS, however, are not as low as those seen in classical GHD. This could be explained by the observation that some studies have found a positive correlation between BMI and IGF-I levels in healthy obese children ($r = 0.30$, $p = 0.05$) [48] and adults [53, 56]. Factors involved in childhood obesity, most importantly caloric and protein intake [57] and insulin secretion [58], may increase serum concentrations of IGF-I. Therefore we suggest that the decrease in IGF-I caused by hypothalamic GHD in PWS may be partially counteracted by the metabolic changes of adiposity.

Argument 5: Insulin Secretion in PWS Is Decreased as in GHD

Insulin levels in healthy obese children are elevated (e.g. 121.2 pmol/l in obese children and 60.2 pmol/l in controls) [19, 59]. Therefore, a fifth argument in favour of GHD in PWS is provided by decreased plasma insulin levels.

In the past, little attention was given to insulin levels in PWS children. It was thought that the metabolic characteristics of PWS obesity did not differ from those of exogenous obesity, which is characterized by hyperinsulinaemia and insulin resistance [60], leading to non-insulin-dependent (type 2) diabetes in some adolescents and adults. It was reported that 3 of 5 adults with PWS initially described by Prader fulfilled the criteria of type-2 diabetes [61], and that the majority of patients presented with high plasma insulin levels [62]. At the same time, in this study, low insulin levels were found in some young children with PWS, which were attributed to the absence of obesity.

Meanwhile, insulin levels have been reported to be low in PWS as opposed to simple obesity: fasting insulin levels were significantly lower in PWS children (35.8 pmol/l, $p < 0.01$) than in healthy obese controls (124.0 pmol/l) [63]. Decreased responses to an oral [64] and an intravenous glucose [63, 64] load were found in children and adults with PWS compared with healthy obese controls. The reduced β-cell response was ascribed to the hypothalamic GHD. In our study, not only the non-obese young children (14.90 pmol/l, –0.8 SD) but even the markedly obese older children (37.7 pmol/l, –0.7 SD, $p = 0.01$) had decreased fasting insulin levels compared with normal-weight reference values [55]. The mean insulin level of the obese PWS children fell markedly below the 2.0- to 2.5-fold elevation seen in non-syndromal obese children [59, 65]. At least in children, these results refute the view that the metabolic characteristics of PWS obesity do not differ from those of exogenous obesity [60, 66]. They also contradict the supposition that insulin levels in PWS are low exclusively before obesity sets in. The presented data, however, show that both under- and overweight prepubertal PWS children have low insulin levels as is the case in classical GHD [67].

However, even in GHD, there might be a threshold of fat mass, especially abdominal fat mass [68], above which insulin secretion is increased and insulin sensitivity altered. We observed an elevated insulin level in 1 pubertal patient who was grossly overweight (BMI 38 kg/m^2). This observation is compatible with the recent hypothesis that insulin resistance in GHD adults depends on the absolute amount of body fat and that BMI has to be at least 27 kg/m^2 to induce obesity-associated insulin resistance and concomitant hyperinsulinism in GHD [67], mediated mainly by increased fatty acids.

Argument 6: Catch-Up Growth with Human GH Therapy in PWS

The influence of exogenous GH on growth dynamics in children with PWS has been analysed in several studies, including our own, and the results provide further arguments for GHD in this type of syndromal obesity.

After 2 years of human GH (hGH) therapy, Angulo et al. [54] reported a significant improvement in height from –2.2 SD before treatment to 0.8 SD in 30 PWS children aged 2–16 years. There was a marked increase in growth velocity from 4.1 cm/year before therapy to 11 cm during the first year of therapy. Lindgren et al. [17] compared the growth of 15 PWS children, aged 3–12 years, during 12 months of hGH treatment with that of 14 untreated PWS controls. Height velocity in the first year increased from –1.9 SD to 6 SD in the treated children, but slowed down in controls from –0.1 SD to –1.4 SD. Height SD only increased in the treated children, from –1.6 to –0.4 SD. In another controlled study, Carrel et al. [30] observed that height, SD significantly rose from –1.1 to –0.6 in 35 PWS children during 12 months of hGH therapy, but remained at –1.5 SD in 19 untreated PWS controls. No significant difference in the progression of bone age was found. During hGH therapy, height velocity increased from –1.0 to 4.6 SD.

Two studies have recently reported on a longer period of therapy of up to 5 years which achieved a roughly similar height gain [69, 70]. After 4 years (fig. 1) of hGH treatment in 18 prepubertal PWS children, height gain reached

1.8 SD, yielding an average height of 0 SD and a normalization of hand and, less markedly, foot length [69]. Mean height velocity in the first year increased in the prepubertal obese children from –1.4 to 8.5 SD and remained above 2 SD throughout 3 years of therapy. During hGH therapy, bone age approached the chronological age. Even though bone age was not clearly retarded before therapy in all cases, a considerable height gain could be observed, confirming that bone maturation before therapy in prepubertal children is not a reliable predictor of the growth response to GH, as recently shown in GHD [71]. Furthermore, prediction of final height markedly improved in the prepubertal children and reached the range of their parental target height despite the average adult height of untreated PWS reported as being reduced to –2.5 SD of reference values [7].

The dramatic increase and maintenance of elevated height velocity as well as the overall height gain during GH therapy (fig. 1a) resemble the catch-up growth encountered in GHD during GH substitution therapy [72, 73]. The growth velocity of children with PWS during GH therapy distinctly exceeds that reported in short-stature patients without GHD even at higher GH doses [74, 75]. Because of a similar increase in hand and foot length and height, these children no longer have small hands and feet and all body proportion parameters are balanced (fig. 1) [69], as happens in treated GHD patients [76].

In summary, GH therapy normalizes growth and body proportions in prepubertal children with PWS. If treatment is instituted early enough, final height prediction will reach the parental target height range after 3 years, and short stature as well as small hands and feet will no longer be present. A growth-promoting effect of exogenous GH of this order has so far only been described in children with GHD.

Are Changes in Body Composition under GH Therapy an Argument for Underlying GHD in PWS?

It has been claimed that longitudinal assessment of body composition in patients who have discontinued GH replacement may provide a reliable means of redefining GHD in young people in the transition from childhood- to adult-onset GHD [77]. Does it therefore follow that in PWS an improvement in body composition under GH therapy defines the presence of GHD? Several studies have reported an increase in LBM and a reduction in fat mass during GH therapy in PWS. However, body composition does not depend solely on GH, but is also modulated by the highly complex signalling system which regulates appetite and energy homeostasis. We will therefore address other factors regulating body composition in PWS apart from GH.

After as little as 6 months of therapy, Davies et al. [78] reported an increase in fat-free mass from 59.4 to 67.5% of body weight in GH-treated PWS patients, measuring body water by stable isotopes. Lindgren et al. [17, 70], as described above, demonstrated that fat mass measured by DEXA decreased from 3.0 to 1.5 SD in GH-treated children in the first year of treatment, whereas it increased in untreated PWS controls, and, in the long term (up to 5 years), fat stabilised near 2 SD. Muscle area, assessed by computed tomography scan of the thigh after the first year of treatment, significantly increased (43–58 cm^2). In a controlled study by Carrel et al. [30], relative fat, analysed by DEXA, decreased from 46.3 to 38.4% and LBM increased from 20.5 to 25.6 kg in 35 PWS children during 12 months of hGH therapy, but there were no changes in 19 PWS controls.

Not only did we observe weight normalisation in prepubertal patients with PWS undergoing long-term treatment with hGH (fig. 1b), but we also measured body composition by DEXA in 16 children with PWS [33]: after 3.5 years of treatment with GH, there was a net reduction in body fat in the prepubertal overweight children (from 2.2 to –0.05 SD compared with US reference values) as well as in the pubertal overweight children (fig. 2, compared with Dutch reference values). As explained in the third argument, we adjusted LBM not only for age and sex but also for height in order to correct for a growth-related increase, and could therefore observe that the initial deficit in LBM (–1.8 SD in prepubertal overweight children) is counteracted by GH only during the first year of therapy (increase to –1.33 SD) [24]; in the long term, GH therapy does not further compensate for this deficit.

As extrapolated from studies in healthy obese adults and in children with GHD, Turner's syndrome or intrauterine growth retardation, the net effects of GH on body composition, induced by lipolysis and protein anabolism, are limited to several weeks [79] or months [40, 80]. Therefore, it is remarkable that GH induces sustained metabolic effects in PWS. Moreover, data on the metabolic effects of GH in children are scarce and changes in body composition seem to be independent of prior endogenous GH secretion or the dose of GH administered [40, 81], in contrast to the effects of GH administration on longitudinal growth. Hence, it should be emphasized that the dose dependency of the effects of GH on muscular and fat tis-

sue has not yet been investigated in children. The doses used in the PWS studies in general are between 0.03 and 0.04 mg/kg per day, i.e. 1.5-fold that administered for substitution in GHD [82].

Factors other than GH may underlie the changes in body composition in PWS, i.e. nutrient intake for fat mass and physical activity for muscle mass, the main component of LBM. Studies in obese adults have shown that GH at a dose of 0.01–0.05 mg/kg per day has a clear fat-reducing effect if nutrient intake is modestly reduced or kept constant [83–86]. This might also explain why in studies controlling dietary intake of children with PWS during GH therapy [17, 33], reduction of adiposity is greater than in those not controlling energy intake [87]. Likewise, physical activity has been shown to be indispensable for complete muscle growth. Even if the anabolic action of GH is efficient in untrained or hypotrophied muscles, normalisation of muscle mass under GH substitution in GHD will occur only with exercise [88], at least in adults. In this context, PWS children benefit not only from an increase in LBM, but also from the increased physical performance and muscle strength [24, 30], although insufficient to normalize LBM.

We can conclude that the improvement in body composition during GH therapy results from several different therapeutic interventions. It cannot be used as an argument for the metabolic effects of GH alone or as the result of substituting the underlying GHD.

Conclusion

The aim of this article was to identify arguments for the presence of genuine GHD as a part of PWS. Decreasing growth velocity despite the onset of obesity, reduced LBM in the presence of adiposity, small hands and feet, relatively low IGF-I and low insulin levels, as well as the dramatic effect of GH treatment on growth are arguments in support of the presence of hypothalamic GHD in PWS. Even though it might be difficult to ultimately prove GHD in PWS because of the obesity-induced counterregulation, several arguments strongly suggest that the hormonal situation differs from that in simple obesity. GHD on its own may account for several features of PWS. GH therapy dramatically changes the phenotype of PWS in childhood: height and weight become normal and there is a sustained impact on the net loss of body fat. The disappearance of the obese phenotype of the prepubertally GH-treated child relieves the patients and their families of the stigmatisation that they would otherwise endure.

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