A Comprehensive Team Approach to the Management of Patients with Prader-Willi Syndrome

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ABSTRACT

Prader-Willi syndrome (PWS) is a genetic disorder characterized by extreme obesity accompanied by other, multisystem clinical manifestations encompassing both physical and behavioral/cognitive abnormalities. The multidimensional problems of patients with PWS cannot be treated with a single intervention and benefit from a team approach to management to optimize outcomes. Childhood stature below target height and reduced final height are some defining characteristics of PWS, and compelling evidence from growth hormone (GH) treatment trials suggests that hypothalamic GH deficiency exists. Treatment with GH has been shown to increase height velocity in children with PWS, decrease weight-for-height index values and body fat mass, and have a positive effect on lean body mass during at least the first year of therapy. In addition to medical concerns, the behavioral manifestations, including an uncorrectable deficit in appetite control, and cognitive limitations associated with PWS, require long-term multidisciplinary management.

KEY WORDS

growth, growth hormone, metabolic disturbance, behavioral problems, congenital disorders, obesity, Prader-Willi syndrome

INTRODUCTION

Prader-Willi syndrome (PWS), first described in 1956, is a complex multisystem congenital disorder associated with an abnormality of genetic material on chromosome 15. It is characterized by reduced fetal activity, infantile hypotonia, and failure to thrive in infancy followed by the emergence of hyperphagia and development of severe obesity in childhood. Also characteristic of PWS are developmental and speech delay/cognitive dysfunction, cryptorchidism, hypogonitalism/hypogonadism, a particular facial appearance (narrow forehead, almond-shaped eyes, triangular mouth) that is present at or soon after birth, short stature, small hands and feet, strabismus, and behavioral and psychological problems including compulsive behavior and skin-picking. The multiple clinical abnormalities associated with PWS suggest underlying dysfunction in several hypothalamic centers, including those concerned with energy balance, temperature regulation, and secretion of pituitary hormones, including gonadotropins and growth hormone (GH).

The prevalence of PWS has been estimated in several studies conducted in the United States, Sweden and Japan. Prevalence estimates in the range of one in 5,000 to one in 15,000 are obtained when data from these studies are converted to similar units and adjustments are made for recent improvements in life span. In one recently reported population-based study, the birth incidence of PWS was estimated at one in 22,000 and the death rate at 3% annually in the UK. Until the early 1980s, death due to cardiorespiratory complications of morbid obesity often occurred in mid to late adolescence, but, in recent years, life expectancy has been extended as improved methods of management have been developed. Respiratory complications,
however, remain a major source of morbidity, and nearly 50% of people with PWS across all age groups have a history of recurrent respiratory infections\textsuperscript{16}.

**PRADER-WILLI SYNDROME: A GENETIC DISORDER**

In most cases, PWS is a *de novo* defect caused by a lack of expression of normally active paternally inherited genes in the 15q11-q13 region of chromosome 15\textsuperscript{17}. When these genes are maternally inherited, their expression is suppressed by genetic imprinting, a phenomenon by which expression of a gene is modified according to the sex of the originating parent. Through genetic imprinting, the PWS-relevant genes in region 15q11-q13 of the maternal chromosome are inactivated by methylation of the cystine bases in their DNA, while the same genes on the paternal chromosome remain unmethylated\textsuperscript{17}.

Three distinct genetic abnormalities in the 15q11-q13 region of chromosome 15 have been identified in individuals with PWS\textsuperscript{17}. In approximately 70%, there is a small deletion of critical genetic material in the 15q11-q13 region on the paternally derived chromosome\textsuperscript{1}. Most of the remaining 30% of individuals with PWS have two maternal chromosomes 15 and no paternal chromosome 15, which is designated maternal uniparental disomy 15\textsuperscript{17}. Approximately 1-5% have an imprinting defect, manifested as failure to maintain activation of the 15q11-q13 region of the paternal chromosome, caused by a very small deletion or other abnormality in the center controlling imprinting in this region\textsuperscript{17}. All three of these genetic abnormalities may be detected by methylation analysis\textsuperscript{17,18}.

**CLINICAL MANIFESTATIONS AND COURSE**

The clinical manifestations of PWS include both physical and behavioral/cognitive abnormalities\textsuperscript{7}.

**Physical characteristics**

Infants with PWS are severely hypotonic\textsuperscript{5} and have an abnormal cry. Genital hypoplasia, cryptorchidism, and scrotal abnormalities are common in affected male infants\textsuperscript{7}. The characteristic facial appearance, which may be present at birth, becomes more pronounced with age\textsuperscript{7}. Feeding difficulties, related to both hypotonia and a poor sucking reflex, are common in infancy, as is failure to thrive\textsuperscript{19}. Although hypotonia improves around 8 months of age, attainment of gross motor development milestones, such as sitting and walking, is substantially delayed, and speech development is also retarded\textsuperscript{17,20,21}.

When children are between 1 and 4 years of age, the clinical features of PWS change dramatically\textsuperscript{7}. Difficulties in feeding are replaced by an insatiable appetite for food and excessive food intake. This, together with the decrease of energy expenditure due to reduced physical activity and lean mass, leads to obvious obesity between the ages of 3 and 5 years\textsuperscript{5}. Growth retardation, a symptom of the hypothalamic GH deficiency (GHD), becomes evident in many children with PWS between the ages of 3 and 13 years, and pubertal growth is reduced\textsuperscript{22}. Almost all patients with PWS have abnormally high weight-for-height (W/H) index values after age 10 years\textsuperscript{22}. Even young underweight children with PWS have elevated skinfold standard deviation scores (SDS) when compared with a reference group matched for age and body mass index (BMI), suggesting that body fat is already increased\textsuperscript{23}.

Musculoskeletal problems are common in individuals with PWS\textsuperscript{24-26}. Scoliosis and/or kyphosis may develop as a consequence of hypotonia but may not be evident, even radiologically, until children are between 5 and 10 years old\textsuperscript{24}. Among 24 PWS patients aged 15 to 29 years, scoliosis was present clinically in 15 (62%) and radiologically in 14 of the 15 (58%)\textsuperscript{24}. In another series, 32 of 37 (86%) individuals with PWS were found to have scoliosis of at least 10 degrees, and one of 14 (7%) adolescents and five of ten (50%) adults were found to have kyphosis\textsuperscript{7}.

The incidence of hypothyroidism among individuals with PWS is not known, but thyroid function appears to be normal in most\textsuperscript{28}. Nevertheless, since PWS appears to be a hypothalamic disorder, the hypothalamic-pituitary-thyroid axis could be affected. Levels of thyroid hormone could be low in the
absence of an increase in thyroid stimulating hormone owing to a dysfunction of hypothalamic control of thyroid-releasing hormone secretion.

There is a wide variation in the onset and extent of sexual maturation in patients with PWS. Abnormalities in reproductive function have generally been attributed to a hypothalamic defect, which is most commonly expressed as a deficiency in gonadotropin hormone secretion. Pubertal development is usually delayed, incomplete, or absent. In girls with PWS, breast development is fairly common but menarche may be delayed or absent, and menstrual cycles, if present, may be irregular. Two live births to women with confirmed PWS have been reported, however. A few cases of true precocious puberty have also been reported in patients with PWS. These cases may be due to the variability of hypothalamic lesions, allowing also for precocious stimulation of pubertal development. More common is the early appearance of pubic and axillary hair, which is most likely caused by the obesity-related premature activation of adrenal secretion of androgens.

**Cognitive and behavioral characteristics**

Hyperphagia, obsession with food, and food-seeking behaviors are distinctive clinical features of PWS. Hyperphagia appears to be related to an impaired satiety response. As compared with age- and sex-matched control subjects, for example, persons with PWS continued to eat for a longer period and to consume many more calories before satiety was reached when allowed free access to food for 1 hour. Persons with PWS were also found to eat more slowly than normal and obese control subjects but at a non-decelerating rate and for a longer period when food was freely available.

Patients with PWS also have cognitive and behavioral abnormalities other than those related to eating or to food seeking and hoarding. Mental retardation, generally in the mild-to-moderate range, is usually present. Deficits in short-term memory and sequential processing are present but may be balanced by strengths in reading and long-term memory. Speech development is retarded and language ability remains reduced into adulthood in some patients, which further impairs the socialization capabilities of people with PWS. Characteristically, patients with PWS suffer from a disturbed oral motor function with impaired articulation and a high-pitched voice. This may result from abnormalities of the laryngeal anatomy as well as from muscle hypotonia. Speech fluency may also be reduced, but there is no clear pattern of stuttering. There is some evidence that the impaired abilities in grammar and comprehension are associated with mental retardation, as found in a study comparing 11 individuals with PWS, aged 4 to 25 years, with controls matched for age, obesity, and IQ.

Although infants and toddlers with PWS are generally described as happy, affectionate, and easy going, personality changes are noted in older children and adults, who may be prone to temper outbursts, violent acts, oppositional behavior, and obsessive-compulsive behaviors such as skin-picking, hoarding, ordering, and arranging. Initially, abnormal behavior is usually related to food and the withholding of food, but it becomes independent of eating later in life. The incidence of compulsive behaviors is greater among patients with PWS than among patients with mental retardation caused by other disorders, and certain symptoms (thinking about hoarding, recurrent need to tell or ask) are more common in patients with PWS than in those with obsessive-compulsive disorder. Affective disorders, which may be marked by psychotic symptoms, appear to be more common among adult patients with PWS than among other groups with intellectual disabilities.

**SHORT STATURE AND ABNORMAL BODY COMPOSITION: ROLE OF GROWTH HORMONE**

Growth retardation becomes evident in many children with PWS after age 3 years, and short final stature is noted in many adults with PWS. Children with PWS generally become clinically obese between 3 and 5 years of age, and although obesity may advance skeletal maturation in children with PWS, the weight gain is not accompanied by the degree of acceleration of bone age and growth observed in healthy obese children. Abnormalities in body composition, which include increased total
fat mass, decreased lean body mass, and anomalies in the distribution of adipose tissue, become more marked with age, although abnormal body composition is detected in infancy before clinical obesity is present. The reduction in lean tissue mass in children with PWS differs characteristically from the increased lean mass in healthy children with simple obesity.

The growth pattern of children with PWS has similarities to that observed in children with GHD - slow growth and retardation in bone age - when adjusted for the presence of obesity, which characteristically accelerates growth and advances bone age. The body composition abnormalities characteristic of PWS are also similar to those observed in GHD.

In one recent study, 40 of 44 PWS patients showed low peak GH values, as measured with the use of standard provocative stimulation tests with insulin, clonidine, or L-dopa, and 43 had blunted 24-hour GH secretion. However, the endocrine assessment of GHD in PWS is complicated by the presence of obesity, which itself causes abnormalities in GH secretion. Spontaneous or provoked GH secretion in patients with PWS is generally lower than that observed in healthy non-obese subjects but similar to that seen in healthy obese controls.

Serum insulin-like growth factor-I (IGF-I) levels are also often low in children with PWS, in contrast to healthy obese children, in whom serum IGF-I levels are generally normal or high in the presence of reduced levels of GH. In addition, low GH and IGF-I levels are found not only in PWS patients who are severely obese but also in those who are of normal weight, in contrast to healthy obese children, in whom IGF-I levels have been shown to correlate with BMI. These findings suggest that the low levels of GH and IGF-I in patients with PWS are not simply a reflection of obesity.

Although the obesity-induced counterregulation of GH secretion makes it difficult to establish the presence of GHD in PWS through endocrine assessments, the results of GH treatment trials in patients with PWS suggest that GHD may explain several features of PWS. This evidence is further supported by the positive impact of GH therapy on growth, body composition, and other characteristics in patients with PWS; the results of these studies are discussed below.

HYPERPHAGIA AND ENERGY BALANCE DISTURBANCES: EVIDENCE FOR HYPOTHALAMIC DYSFUNCTION

The clinical features of PWS are consistent with the hypothesis that this disorder involves an underlying hypothalamic dysfunction. It is speculated that hyperphagia, a defining characteristic of PWS, may be related to decreased numbers of oxytocin-secreting neurons in the paraventricular nucleus of the hypothalamus. Oxytocin is known to inhibit food intake and gastrointestinal motility and is thought to play a role in satiety in rats. Clinical studies suggest that the hyperphagia associated with PWS may be related to a defect in satiety rather than to increased hunger, as shown by the lack of deceleration in the eating rate and longer time to satiation. It has also been suggested that the abnormal satiation response to food may be related to elevated γ-aminobutyric acid levels in the satiety center in the ventromedial hypothalamus.

Serum levels of ghrelin, a peptide hormone that stimulates GH secretion and increases food intake, are highest among obese persons with PWS. In a recently reported study, fasting serum ghrelin levels were measured in 13 obese PWS children and compared with levels in control groups that included normal-weight and non-PWS obese children. Compared with BMI-matched controls, children with PWS had fasting ghrelin concentrations that were significantly higher (mean ± SD: 429 ± 374 versus 139 ± 70 pmol/L; p <0.001). The investigators concluded that elevation of serum ghrelin levels may play a role as an orexigenic factor in patients with PWS and may be the driving force underlying their insatiable appetite.

Energy balance is typically abnormal in PWS for two reasons. First, energy expenditure both at rest and during sleep is reduced, owing to the decrease in fat-free mass, and second, total energy expenditure is reduced, owing to the low activity levels documented in individuals with PWS. GHD, which is known to decrease lean
body mass and increase fat mass, may contribute to the dysregulation of energy balance in PWS. It has been known for some time that energy requirements of patients with PWS are approximately half those of healthy individuals.

The morbidity accompanying the obesity is a key factor in the mortality of PWS patients. Cardiovascular risk factors are already increased in children with PWS. Premature coronary artery atherosclerosis in a morbidly obese 26 year-old male with PWS and type 2 diabetes mellitus has been reported, and a well-known relationship exists between obesity and sleep apnea, coronary artery disease, type 2 diabetes mellitus, and atherosclerosis, all of which can contribute to mortality in these patients. Butler et al. studied 66 persons with PWS with a mean age of 19 years (range 0-46 years) and reported a prevalence of non-insulin-dependent diabetes mellitus of 25% in adults, and high rates of respiratory infections, fractures, leg ulcerations, sleep disorders and severe scoliosis.

One recently reported study of 19 adult patients with PWS found that four were hypertensive, one had heart failure and diabetes mellitus, four had impaired glucose tolerance, and seven had modest dyslipidemia. Fifty percent had severe GHD, and the risk factors in the study predicting cardiovascular disease were interpreted as secondary to GHD.

A TEAM APPROACH TO MANAGEMENT

PWS is a complex multisystem disorder marked by symptoms, medical complications, and behavioral problems that evolve over time. The multidimensional problems of patients with PWS benefit from a team approach to management. This review focuses on the effects of GH therapy on stature, body composition, and metabolic disturbances in patients with PWS, and on management of their behavioral problems. Genotropin (somatropin [rDNA origin] for injection; Pfizer) is approved for long-term treatment of growth failure in pediatric patients with PWS in Europe, Japan, and the United States. The goals of GH treatment include reduction of W/H to the normal range, reduction of fat mass, increase of lean body mass, and normalization of final height and body proportions. To achieve an improvement in body composition and general health, planned weight-management programs for those with PWS must include caloric restriction, dietary supervision, and education, as well as psychosocial support for parents and caregivers, but avoidance of undernutrition during infancy; a daily exercise program and physical therapy to improve muscle hypertonia and scoliosis; appropriate behavioral and psychotropic interventions; and speech therapy. Screening for breathing disorders and adequate treatment of respiratory infections are fundamental in the management of PWS. Finally, the multiple cognitive and behavioral dysfunctions associated with PWS require lifelong management.

MANAGEMENT OF GROWTH AND BODY COMPOSITION ABNORMALITIES

Childhood stature below target height and compromised final adult height are defining characteristics of PWS. Although hypothalamic GHD is difficult to confirm in patients with PWS because obesity interferes with diagnostic testing, compelling evidence from GH treatment trials suggests that this defect exists.

Effect of GH and energy input on linear growth

In the 1970s and 1980s, exploratory studies in small numbers of children with PWS and short stature indicated that GH treatment usually had beneficial effects on growth. During the 1990s, the effect of GH treatment on growth in children with PWS was evaluated in a number of clinical trials in which treatment continued for at least 1 year and sometimes for 3 or more years.

Treatment with GH has been shown to increase height velocity SDS in children with PWS in numerous studies. The effect of GH treatment is most clear-cut in prepubertal children who are not underweight at the initiation of therapy, and it resembles the catch-up growth encountered in GHD during substitution therapy.

The short- and long-term effects of GH therapy plus dietary management in children with PWS have also been evaluated in several randomized...
trials75–78 as well as in an ongoing long-term open Swiss treatment trial initiated in 1994 that is enrolling children between the ages of 0.3 and 14.6 years75,76,77. In the Swiss study, the beneficial impact of GH on linear growth is evident in prepubertal overweight children with PWS (Fig. 1a). These children had significant (p <0.05) increases over baseline height velocity SDS at 6, 24, and 36 months, although the change in height velocity SDS was most notable during the first 6 months of treatment. There is also evidence of benefit in young underweight children (Fig. 1a) and in pubertal children74.

In a randomized controlled Swedish trial, a group of 15 prepubertal children with PWS who underwent GH treatment had a significant (p <0.05) increase in height SDS (+1.2 SD) while the control group (n = 12) had a non-significant decline in height SDS (-0.1 SD) after 1 year75. During year 2 of this study, the first group continued GH while the former control group started GH therapy. After completion of year 2, GH treatment was discontinued for 6 months, restarted in a random sample of nine patients from the treatment group and nine patients from the former control group, and continued for an additional 2.5 years78. During the second year of the study, height SDS increased significantly over baseline in both treated groups; height SDS declined slightly during the 6-month off-treatment period and then increased at a lower rate for the remaining treatment period, with final mean height SDS exceeding 0 in both groups78.

In a US study, 54 children with PWS and decreased height velocity SDS were randomized to treatment with GH (n = 35) or to no treatment (n = 19)75. After 1 year, the GH treatment group had a mean height gain of 0.5 SDS and the untreated group had a mean height loss of 0.1 SDS; the difference was significant (p <0.01)75. After year 2 of GH treatment, the 35 treated children had a height velocity SDS of 2.2 ± 2.275. This was a decline from the height velocity SDS of 4.6 ± 2.9 in year 1 but still above the height velocity SDS (-0.7 ± 2.50) of the former untreated group75. In this same group of children, those who received an increased dose of GH during the third year of treatment had a significantly (p <0.05) better growth rate than either those who remained on the same dose or those who received a reduced dose77.

Although improvement in height is not the main goal in the management of PWS, these findings document the efficacy of GH treatment in this syndrome. Possible adverse effects of GH treatment in patients with PWS are currently being studied7. Scoliosis is exacerbated by rapid growth in children without PWS. Because, in addition, PWS appears to be associated with an increased risk of scoliosis, all children with PWS should be carefully monitored for scoliosis regardless of GH treatment. Because obesity is a major risk factor for non-insulin-dependent diabetes mellitus and GH treatment is known to increase insulin resistance, all obese children with PWS should be carefully monitored for glucose intolerance and diabetes mellitus whether or not they are being treated with GH63.

Effect of GH, energy intake, and physical activity on body composition

Body composition abnormalities in PWS are determined by multiple factors, including age, physical activity, GH secretory status, and energy balance49,54,60,85. Treatment with GH has been shown to decrease W/H SDS and body fat mass in children with PWS who are obese at the initiation of therapy73,76,77,79. Lean mass also increases during the first year of GH treatment, but even continued treatment does not completely compensate for the initial deficit in lean mass53,73,75,77,85.

In the Swiss study, 12 children with PWS, aged 3.7 to 14.6 years, were treated with GH for 3.5 years85. There was a marked loss of fat mass (Fig. 2a), which was still significant after 2 years. This trend was also reflected by W/H, which declined significantly after 6, 24, 36, and 42 months of treatment (p <0.05; same prepubertal overweight group as in Fig. 1b)85. Mean lean mass was -2.95 SD at baseline and increased significantly (p = 0.005) to -1.79 SD at 12 months (Fig 2b). When lean mass was adjusted for height, no gains were observed after 6 months of GH therapy7, demonstrating that the lean mass increase was related to catch-up growth rather than to an increase in muscle mass85.

In the US study, 35 (32 prepubertal, three pubertal) children with PWS, aged 4 to 16 years,
Fig. 1: a. Height standard deviation score (SDS) and b. weight-for-height SDS of children with Prader-Willi syndrome, referring to normative data of the Zurich Longitudinal Study, before and after up to 5 years of growth hormone therapy for young, initially underweight children treated up to 48 months (triangles) and prepubertal overweight children (squares). Shown are medians (solid lines) as well as the minima and maxima for the combined group (broken lines). Significant differences (tested at 6, 48, and 60 months by the Wilcoxon test) in each group versus the value before therapy are indicated as * (p <0.05). Adapted with permission from Eiholzer U, Bachmann S, l'Allemand D. Is there growth hormone deficiency in Prader-Willi syndrome? Horm Res 2000; 53 (Suppl 3): 44-52. © 2000 S. Karger AG, Basel.

Fig. 2: a. Fat mass and b. lean tissue mass measured by dual-energy X-ray absorptiometry in overweight children with PWS, as standard deviation scores (SDS) corrected for height, compared with Dutch children. Shown are medians (solid lines) and individual courses before and during therapy with growth hormone in prepubertal overweight (fine lines) and pubertal PWS children (dotted lines). Significant differences indicated as * (p <0.05) and ** (p <0.01). Data from Eiholzer U, l'Allemand D, van der Sluis I, Steinen H, Ellis K. Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy. Horm Res 2000; 53: 200-206.
were treated with GH for 2 years. Body fat percentage decreased only in the first 12 months and remained stable in the next 12 months. However, mean body fat percentage at both time points was significantly reduced from baseline (46.6% vs 39.9% vs 49%)[76]. At 12 months, mean lean mass was significantly greater than at baseline in the GH-treated group (25.6 kg vs 20.5 kg; p < 0.01)[75]; after 24 months, mean lean mass remained significantly greater than at baseline (28.5 kg vs 22.9 kg; p < 0.01)[76]. When patients were randomized to treatment with standard-, high-, or low-dose GH in the third year, only the high-dose group had a numerical, but not statistically significant, decrease in body fat percentage (40% vs 37%)[77].

Available evidence suggests that GH treatment may help to improve the abnormalities in body composition characteristic of PWS. The results of GH treatment studies indicate that lean body mass increases[77,77] and body fat mass decreases[77,77] during the first year of therapy, when the greatest change occurs[76,77]. With continuing GH therapy, fat mass generally stabilizes[76,77] and relative fat[76,77] or BMI[77] remains below the initial levels. The assessment of the continued efficacy of GH therapy on lean body mass may depend on how lean body mass is calculated. Although net lean body mass increased during the second year of therapy in two studies[76,77], the increase in measured lean mass was corrected for growth-related increase in only one of them, and stabilization of lean mass was observed after 6–12 months[75]. In a continuation of these studies, net lean body mass did not increase during a third year of GH treatment[77,77], even when a higher dose was used[77].

These findings imply that GH treatment alone cannot engender a lasting improvement in body composition; several behavioral changes are also required[77]. First, to increase muscle mass, the level of physical activity, which is inherently low in individuals with PWS (see below), must be increased[62]. Physical training has been shown to be indispensable for complete muscle growth[88] and therefore constitutes a key component of a comprehensive care program[52,77]. Second, GH treatment should be combined with a reduction in energy intake[6,87]. As deduced from findings in simple obesity, a clear-cut fat-reducing effect has been demonstrated only if dietary intake is modestly reduced or kept constant[89,90]. With respect to reduction of obesity, studies in which GH is combined with dietary control[73,75,76,78] produce better outcomes than those without dietary control[79]. Thus, the nutritionist and physical therapist play essential roles in optimal somatic therapy for children with PWS.

MANAGEMENT OF METABOLIC DISTURBANCES

Energy balance

Energy expenditure is significantly reduced in patients with PWS[91,92]. In a recent study, 17 children and adolescents with PWS, aged 7.5 to 19.8 years, had a significantly lower mean basal metabolic rate (BMR) (5.36 ± 1.18 vs 6.38 ± 1.55) and mean sleeping metabolic rate (4.62 ± 1.08 vs 5.60 ± 1.52) than healthy obese control subjects matched for sex and bone age[54]. The difference in BMR between PWS patients and healthy controls disappeared when BMR was expressed as a function of fat-free mass, indicating that the significantly lower (p < 0.05) fat-free mass in the PWS group (27.5 ± 9.9 kg vs 35.9 ± 13.4 kg) was responsible for the reduced energy expenditure[54].

In the 35 prepubertal patients with PWS in the US study, fat utilization, as measured by the respiratory quotient (RQ), was in the lower normal range, which is typical for persons with GHD[75,77]. Mean RQ declined significantly during 3 years of treatment with GH (1 mg/m²/day [−0.03 mg/kg/day])[75,77] and was below the levels of an untreated PWS control group after the first year (p < 0.01)[75]. This finding suggests that GH therapy limits fat stores by promoting utilization of fat for energy[75]. However, total resting energy expenditure was not increased during the first year of treatment[75], although a trend toward improvement was noted in the second year[76].

In summary, energy balance in PWS is impaired both by reduced lean body mass and by GHD with low fat utilization. GH therapy has been shown to have a positive effect on lean body mass at least during the first year of treatment[73,75,77,77] and on fat...
utilization, thereby positively affecting energy balance.

However, GH therapy alone is insufficient to manage energy balance. Surveys have indicated that the baseline energy requirement in those with PWS not receiving GH is estimated to be 50% of the requirement of healthy individuals. During GH treatment, caloric intake may be increased somewhat without weight gain. Nevertheless, in young non-obese children with PWS undergoing GH treatment (18 IU/m²/week [0.025 mg/kg/day]), caloric requirements for weight maintenance were still reduced by approximately 25% compared with those of age-, height-, and weight-matched control subjects. As management of energy balance during GH therapy requires continued dietary control, with restriction of total daily calories and an appropriate balance among protein, carbohydrate, and fat macronutrients, a nutritionist must be included on the therapeutic team.

**Carbohydrate metabolism and insulin levels**

Early descriptive reports of PWS noted that glucose intolerance or diabetes mellitus was present in a fairly high proportion of patients. Obesity in otherwise healthy individuals is linked to an increased risk of insulin resistance and type 2 diabetes mellitus, and it was assumed that similar mechanisms were involved in elevating the incidence of diabetes mellitus among patients with PWS. In contrast to subjects with simple obesity, obese children with PWS have been shown to have reduced fasting insulin and first-phase insulin secretion following a glucose challenge and reduced peak insulin secretion.

Because GH replacement therapy has been shown to elevate insulin resistance and insulin secretion markedly in patients with GHD, there has been some concern that treatment with GH might accelerate the manifestation of diabetes mellitus in predisposed patients with PWS. Elevated 2-hour plasma glucose levels after glucose challenge have been found in some children with PWS both before and after GH therapy.

In one controlled, randomized trial in Sweden, glucose and insulin homeostasis in 19 prepubertal children with PWS before and during treatment with GH was compared with that in 11 healthy obese control subjects. The PWS children were treated with GH at a dose of 0.033 mg/kg/day for 2 years (n = 10) or with GH at a dose of 0.066 mg/kg/day for 1 year (n = 9). At baseline, children with PWS had lower fasting insulin levels and reduced first-phase insulin secretion compared with control subjects. After 1 year of GH therapy, insulin levels increased significantly in the PWS groups (p < 0.001), but glucose utilization remained normal.

Six children in the group receiving 0.066 mg/kg/day exhibited fasting hyperinsulinemia after 1 year of GH therapy. After 5 years of GH therapy, fasting insulin levels were normal in the group treated with 0.033 mg/kg/day throughout the study. In the group receiving 0.066 mg/kg/day during the first year of GH therapy, six patients developed hyperinsulinemia, although they had been switched to the lower dose of 0.033 mg/kg/day. Two children in this group developed type 2-like diabetes mellitus during a period in which their BMI increased from +2 to +3.7 SDS and from +5.9 to +7.1 SDS, respectively, probably owing to poor dietary compliance.

In the Swiss long-term study, in which 17 children with PWS, aged 1.5 to 14.6 years, received GH (24 IU/m²/week [0.037 mg/kg/day]) for 3 years, glucose tolerance was always within the normal range. In addition, the 120-minute glucose level improved significantly during GH therapy; in one prepubertal obese boy with glucose intolerance at baseline, glucose tolerance normalized during GH therapy. Fasting insulin was low in comparison with reference levels in both underweight and obese patients before GH treatment, rose significantly after 1 year of GH therapy, and returned to initial levels at 3 years. First-phase insulin secretion after glucose challenge was low in comparison with obese reference values, increased during GH treatment. However, maximum insulin secretion was delayed both before and during GH therapy in comparison with both lean and obese reference values. This pattern of insulin secretion does not appear to be the result of GHD in patients with PWS, as it is unaltered during GH therapy. The mechanism by which diabetes mellitus develops in patients with PWS is not known at present but may involve the delay in secretion and release of insulin.
compounded by obesity-induced insulin resistance. Blood glucose levels should be monitored on a regular basis in patients with PWS. Changes in carbohydrate metabolism induced by GH therapy seem to be transient, unless patients are receiving a high GH dose or have excessive weight gain.

**Cardiovascular risk factors**

Obesity is the main cause of morbidity and mortality in patients with PWS. Simple obesity is associated with the presence of other risk factors for cardiovascular disease, but the relationship between obesity and cardiovascular risk has not been studied in patients with PWS. However, as can be deduced from a recent study, the amount of visceral fat tissue is lower in women with PWS than in control women with the same BMI. This implies that major factors enhancing the risk of cardiovascular disease are different from those in non-syndromal subjects with the same degree of obesity.

Similar conclusions were drawn from a Swiss study in children with PWS. Relative fat mass, waist/hip circumference ratio (WHR), and lipid and lipoprotein levels were measured before and after the initiation of GH therapy in 23 patients: nine children (aged 0.3 to 4.1 years) were underweight at baseline; nine (aged 3.7 to 9.5 years) were pre-pubertal and overweight; and five (aged 9.0 to 14.6 years) were pubertal and overweight. At baseline, the mean relative fat mass was above the upper limit of the normal range in all overweight children, WHR was >90th percentile in 35%, and plasma lipids were abnormal in up to 35%. After GH treatment (24 IU/m²/week [0.037 mg/kg/day]) for a mean of 3 years, relative fat mass decreased significantly from baseline values (p <0.001) and WHR became normal in all patients. The increased fat mass, abnormal WHR, and prevalence of lipid abnormalities in children with PWS prior to initiation of GH therapy were similar to findings in patients with untreated GHD. GH treatment improved fat mass, normalized WHR, and reduced the prevalence of lipid abnormalities to within the normal range. No correlation was found, however, between lipid values and total fat mass or WHR. This suggests that GH has a direct effect on lipid metabolism, as has been observed in adults receiving GH for GHD. Because GH therapy is not recommended in adults with PWS unless they meet the criteria for GHD, routine monitoring of lipids is recommended, and lipid-lowering treatment may be appropriate in adults with elevated levels of total or low-density lipoprotein-cholesterol or low levels of high-density lipoprotein-cholesterol.

**Respiratory dysfunction**

Abnormal responses to hyperoxia, hypoxia, and hypercapnia have been noted in patients with PWS. An increased incidence of sleep-related breathing disorders has been reported in obese children and adults with PWS, including sleep apnea, daytime sleepiness, daytime napping, snoring, restless movements during sleep, and cataplexy. Sleep abnormalities independent of disordered breathing have also been reported and may reflect underlying hypothalamic dysfunction. However, obesity alone is inadequate to explain the decreased sensitivity of peripheral chemoreceptors to changes in blood oxygen and carbon dioxide content. Only recently, a primary disturbance of central respiratory control was demonstrated in young children with PWS who were not yet obese. Ventilation rate increases less in response to hypoxic or hypercapnic gas mixtures, and a deficient arousal response to hypoxia or hypercapnia during sleep has also been noted. Taken together, these findings indicate a primary disturbance in central respiratory control in PWS, which may be worsened by the development of obesity.

In a clinical trial of the Swedish group, in which nine children with PWS were treated with GH (0.1 IU/kg/day [0.033 mg/kg/day]), minute ventilation volume, tidal volume, respiratory rate, and central inspiratory drive during stimulation with inspired pure oxygen and 4% carbon dioxide were measured before and after 6-9 months of GH treatment. Minute ventilation at rest was significantly increased after GH treatment (p <0.002), as was central inspiratory drive (p <0.04), while the ventilatory response (% change in minute ventilation) to breathing 4% carbon dioxide rose significantly (p <0.02). While GH therapy may have some beneficial effects on ventilatory mechanics, the
mechanism by which GH influences respiratory function in patients with PWS is unknown at present. GH has been found to improve respiratory muscle function in children with PWS. The effect of GH on pulmonary function was assessed using a 12-month, balanced, randomized, double-blind, placebo-controlled crossover study in 12 children with PWS. After 6 months of GH therapy, peak flow rate, percentage vital capacity, and forced expiratory flow rate improved and the number of hypopneic and apneic events and the duration of apneic events trended toward improvement. The investigators concluded that GH intervention may contribute to improved pulmonary function in children with PWS.

Mortality

Few data are available on mortality directly attributable to complications specific to PWS. In a study of persons with PWS in eight counties in the UK, the mortality rate was estimated as 3% per year, compared with an overall death rate of 0.13% per year in the general population of England and Wales up to the age of 55 years.

The cause of death in patients with PWS is often related to respiratory problems. Since chronic respiratory insufficiency may cause cor pulmonale, and this has been described as the main cause of death in those with PWS, polysomnographic investigations and echocardiography should be performed routinely in patients with PWS from childhood.

A series of 27 deaths in patients with PWS without GH treatment ranging in age from neonates to 68 years was reported in 2003. Two main age groups could be distinguished: children up to 5 years of age (n = 13) and adults (19-45 years, n = 13). One boy was 9 years old. Of the 13 children, two died by accidents; nine of the remaining 11 died from respiratory causes: these were hypoventilation, sometimes in combination with aspiration (3/9) and infections (6/9). The clinical course of the respiratory infections in the children was shorter and more acute than anticipated, and death occurred rather suddenly and unexpectedly. None of the children was markedly obese, but all adults were found to be obese. Eleven out of 13 adults died from causes related to complications of obesity. In the remaining cases, death was judged probably not related to PWS.

Seven deaths worldwide of children with PWS using GH therapy have been reported as of June 2003. Two of the deaths during GH treatment occurred in an 8 month-old infant and a 6 year-old child with PWS and respiratory problems from birth. One of the deaths was discovered by post-marketing surveillance, and one was reported by personal communication. Three of the seven deaths were reported among 675 PWS children treated with GH included in the KIGS database (Pfizer's international growth database). One, in a 4 year-old markedly obese boy, occurred 3 months after the start of therapy and was due to aspiration pneumonia and respiratory failure. One, in a grossly obese 8 year-old with obesity/hypoventilation syndrome, occurred 2 weeks after the start of GH treatment. The third patient, a boy of 15.9 years who was also severely obese, was hospitalized for sudden respiratory insufficiency 7 months after the start of GH therapy. He was treated for pneumonia diagnosed radiographically but died shortly afterward.

All of these seven children died in the context of respiratory insufficiency; in five of them respiratory problems were documented before starting GH therapy. At least four of them had pneumonia, but information is scarce about the remaining three. The maximum duration of GH therapy was 3 months in five children; in the remaining two cases it was 5 months and 7 months, respectively. All but the youngest were reported to have been markedly obese. Independently of GH treatment, children with PWS seem to present with more frequent and more serious respiratory problems than do healthy children. From two well-documented case reports of death in an 8 month-old infant and a 6 year-old child, several pathophysiological explanations may be inferred by induction. The pathogenesis of the respiratory problems associated with PWS seems to be multifactorial, including peripheral mechanisms, such as muscular hypotonia, facial dysmorphism, narrow airways, and tonsillar hyperplasia, as well as central mechanisms, such as hypothalamic and chemoreceptor dysfunction.
The decrease in muscle mass in children with PWS may be another important factor. We found reduced fat-free mass in infants with PWS. The decrease in muscle mass, especially the decrease in mass of the respiratory muscles, together with a defect in architecture and function of the throat due to muscular hypotonia, tonsillar hyperplasia, and other factors, may represent the most important possible explanations for disturbed respiration leading to alveolar hypoventilation in these infants. The hypothesis that respiratory muscles are involved in the breathing disorder in PWS has been corroborated in studies of GH treatment in children (see above). Radiological studies of persons with PWS have shown a reduction in cross-sectional area at the oropharyngeal or nasopharyngeal level compared with normal controls. Hyperplastic tonsils in children with PWS, together with a structurally narrowed upper airway, tonsillar infection, and/or hypotonia, may lead to upper airway obstruction and might contribute to sudden death. Hypoventilation with insufficient airflow may also lead to an increased susceptibility to respiratory tract infections.

As noted above, it was demonstrated that GH treatment leads to an improvement in respiratory function and an increase in carbon dioxide sensitivity. It is, however, important to note that a beneficial effect on respiration was demonstrated only after 6 or 12 months of therapy. Our own data showed changes in body composition to be greatest between the third (UE, unpublished data) and the sixth month after initiation of treatment. Five out of the seven deceased children, however, had received less than 3 months of therapy, and, possibly, there had not been enough time to benefit from the anabolic effects of GH on muscle. The fact that all these children died during the first months on GH therapy suggested that such therapy affected mortality in children with PWS - either decreasing mortality after the first months of treatment or increasing mortality during the first months, or both. It is conceivable that GH therapy might increase a pre-existing risk during the first months of treatment. Therefore, in some patients with identifiable risk, treatment with GH might be the intervention of last resort. However, the precise effect of GH in this setting has not yet been determined conclusively. Alternatively, there is evidence that GH therapy indeed improves respiratory function in PWS after some months of administration, thereby providing some protection against hypoventilation. Nevertheless, labeling in the United States for the use of Genotropin® in PWS contains a contraindication and a warning for initiating therapy for the patient with extreme obesity or a history of respiratory distress, indicating that obesity should be approached first by dietary means and respiratory distress treated first before GH is used.

We suppose that in all of the fatal outcomes, a pre-existing ventilatory disorder might not have been given the attention that it should. All of these children might have had hypoventilation with impaired respiratory regulation even before GH therapy was instituted. Before starting GH therapy, polysomnography and an ENT examination, followed, if necessary, by tonsillectomy, should be performed. Airway infections in PWS should be treated aggressively with antibiotics. If fever persists, the child should be monitored carefully until body temperature has returned to normal.

Effect of GH on scoliosis

In a part of the US study including 46 children with PWS, aged 5-16 years, scoliosis progression did not differ significantly between the group treated with 1 mg/m²/day (~0.03 mg/kg/day) of GH and controls during the first year of treatment, and the curve measurement did not change significantly during the second or third year of treatment. In addition, there was no significant difference between GH dosage groups (0.3-1.5 mg/m²/day [~0.01-0.045 mg/kg/day]).

Effect of GH on hypothalamic hypothyroidism

As in patients with GHD without PWS, in some individuals with PWS, GHD may mask central hypothyroidism by leading to a relatively high serum thyroxine (T₄) level. Treatment with GH may thus unmask pre-existing secondary hypothyroidism in some patients with serum T₄ levels in the low-normal range. For these patients, adequate thyroid hormone replacement therapy is needed.
MANAGEMENT OF DEVELOPMENTAL PROBLEMS

The developmental problems of children with PWS evolve with age. Among newborns and infants, severe hypotonia and failure to thrive are the most pressing problems. Muscle hypotonia and difficulty in arousal may contribute to feeding problems of infants with PWS. Early transition from breast to bottle feeding, using bottle nipples with enlarged holes and small, frequent feedings, may help ensure adequate nutrition; short-term nasogastric or orogastric tube feeding may be used if required. During the first 2 years of life, children with PWS are not usually obese, although increased fat stores are already present. Paradoxically, there is a significant risk of undernutrition, on the one hand because of feeding problems, and on the other hand because of the parental fear of obesity. As growth failure would reflect a chronic energy deficit, energy intake should be adjusted to promote growth within the 25th to 75th W/H percentile.

Early childhood

The profound muscle hypotonia of infancy gradually improves with time, and children with PWS generally begin to walk between 2 and 3 years of age. The developmental delay shows a typical pattern, with these children being more retarded on speech and gross motor scales than on other scales. Physical therapy assessment may be useful in identifying motor skill deficits, and a plan to facilitate the development of motor skills should be developed. Early educational intervention and speech therapy are suggested to address delays in cognitive development and speech and language difficulties. When children are between 18 months and 3 years of age, feeding difficulties are replaced by hyperphagia. The goal of dietary intervention for toddlers and young children is to maintain weight at or below the 75th W/H percentile. GH should be given to children <2 years of age only in a treatment trial setting, as data for this age group are incomplete. GH should be given to children <2 years of age only in a treatment trial setting, as data for this age group are incomplete. In any case, especially in this age group, the exclusion of central or obstructive breathing disorders by oxycardiorespirography or polysomnography is a prerequisite for GH therapy.

Middle (prepubertal) childhood

In middle childhood, excessive weight gain becomes a major concern requiring careful management, and food-seeking behavior may become prominent. Children with PWS have reduced energy requirements, necessitating strict control of caloric intake. The recommended daily caloric intake for weight maintenance in PWS children between 3 and 9 years of age ranges from about 700 to 1,400 calories/day and should be related to actual height, amounting to 7.87 to 11.0 kcal/cm (19.98 to 27.94 kcal/inch). The proportion of calories contributed by fats should not exceed 25%. Monitoring of nutritional status is easiest by assessing weight-for-height, which should fall between the 75th and 90th percentiles. In addition, parents should maintain a record of eating and nutrition to facilitate counseling for nutritional behavior.

Social and psychological problems at this age may be related to the common physical features of PWS, including obesity, short stature, and underdeveloped genitalia. When prepubertal children with PWS and growth retardation or short stature are treated with GH, the normalization of height and weight may also improve quality of life, as indicated by anecdotal reports. Abnormal behaviors and personality traits characteristic of PWS emerge during this period; these include preoccupation with food, skin-picking, daytime sleepiness, temper tantrums, stubbornness, and compulsions and rituals. Social skills are often lacking or inappropriate; training, along with other behavioral management programs, can improve cooperation. School performance is often more impaired by behavioral problems than by intelligence.

Adolescence and adulthood

Many adolescents with PWS undergo delayed or incomplete pubertal development. Skeletal maturation is delayed, and the growth spurt generally observed in puberty is usually absent. Although...
GH treatment is generally most effective in normalizing final stature when given to prepubertal children with PWS, pubertal girls with bone age <12 years may experience some benefit. Without exogenous sex hormones, sexual development is usually incomplete, and differences in appearance and maturity can cause emotional distress. Substitution with sex steroids not only may improve physical appearance to peers and increase the pubertal growth spurt but also permits adequate psychosocial maturation. In boys, in addition, it promotes virilization, including deepening of the voice and gain of muscle mass (UE, unpublished data).

Scoliosis is a fairly frequent finding in adolescents and adults with PWS, and surgical correction may be required in severe cases. Complications due to reduced respiratory function and infection have been reported if thoracotomy is required.

Behavior problems tend to intensify with increasing age; skin-picking, preoccupation with food, compulsive behaviors and rituals, stubbornness, and temper tantrums are common. In one study, surprisingly, the severity of obsessive/compulsive-like symptoms and the number of compulsions not related to food among adults with PWS were similar to those observed in age- and sex-matched adults of normal intelligence. A higher incidence of affective disorders has been found among adults with PWS than among adults with intellectual disability of other causes.

Today, with increased awareness about PWS and more active management, many patients with PWS survive into their adult years rather than succumbing to complications of morbid obesity early in life. Most adult patients are unable to live independently, as restriction of access to food is usually necessary to control weight, and out-of-home placement is often required. The family of an adolescent or adult with PWS may have difficulty accepting the need for placement, especially since few group homes can accommodate the special needs of adults with PWS. Transition from high school to a sheltered workshop or supported employment position requires prevocational and vocational counseling that should begin in high school.

Motor development and physical performance

One of the most notable clinical manifestations of PWS in infants and young children is profound muscle hypotonia. Although hypotonia improves with age, deficits in muscle mass, physical strength, and agility are observed in prepubertal children with PWS.

In the US experience, prepubertal children with PWS treated with GH (1 mg/m²/day [-0.03 mg/kg/day]) for 1 year have been shown to have significant improvements (p <0.01) in respiratory muscle strength, lower extremity strength, trunk strength, and upper extremity strength, as compared with their own baseline measurements or with 1-year measurements in a control group of PWS children not treated with GH. Continued treatment with GH for up to 3 years resulted in a sustained benefit on measures of strength and agility.

In an open Swiss study of GH treatment (24 IU/m²/week [0.037 mg/kg/day]) in 12 children with PWS, anaerobic performance, measured on an ergometer, increased during the year of treatment, and parents, physiotherapists, and pediatricians reported an increase in physical activity.

In 10 young Swiss children (aged <2 years) with genetically confirmed PWS, GH treatment (18 IU/m²/week [0.025 mg/kg/day]) was associated with improved scores, compared with baseline, on the locomotor scale of the Griffiths test after 6 and 12 months of treatment. Because this trial did not include an untreated control group, the change in locomotor performance cannot be ascribed to GH treatment and may be associated with spontaneous improvement in muscle hypotonia after infancy. However, these children walked at a mean age of 24.1 months, whereas historical reports put the walking age of children with PWS in the 28-32 month range.

A prospective, controlled Swiss study enrolled 17 children and adolescents with PWS and 18 controls in a daily short calf muscle training program for 3 months. This defined and easy-to-accomplish training program was sufficient to significantly improve local body composition and physical capacity and to lead to a significant increase of spontaneous physical activity. The great importance...
of physical activity should be clearly communicated to parents, other caregivers, and individuals with PWS. It has been suggested that personal and regular physical training programs be created for individuals with PWS, which include a workout of different muscle groups to minimize boredom.

**MANAGEMENT OF BEHAVIORAL, PSYCHOLOGICAL, AND COGNITIVE PROBLEMS**

Multiple abnormalities in behavior, psychology, and cognition are common in patients with PWS. These problems emerge over time and intensify with age. Abnormal behaviors involving food

The insatiable appetite that is a defining characteristic of PWS is accompanied by preoccupation with food as well as by abnormal eating behavior marked by prolonged duration of eating, consumption of excessive calories before reported satiation, a lower initial eating rate, and a lower rate of deceleration of eating rate. Medications used to suppress appetite have not been effective in controlling appetite dysregulation and eating behavior in patients with PWS. Other psychotropic medications, usually given to manage moods and non-food-related behavior, are also generally ineffective in altering eating patterns and may precipitate rapid and excessive weight gain. Chlordiazepoxide did not increase food intake in a controlled trial of 12 patients with PWS and 11 obese controls.

The selective serotonin receptor inhibitors (SSRIs) have been reported to be useful in managing symptoms of affective disorders and conduct disorders but do not essentially change abnormal food-related behaviors. However, in one case report, fluoxetine had positive effects for at least 6 months on weight loss and maintenance in an hospitalized female adolescent with uncontrollable eating and trichotillomania. In six adults and one adolescent with PWS living in a special therapeutic setting, risperidone, an atypical antipsychotic medication, improved severe behavioral problems; five of these patients also experienced weight loss. Weight loss was apparently due to improved behavior and was probably facilitated by the structured therapeutic environment. The investigators urged caution in extrapolating the findings of this small open-label study to children with PWS.

To prevent morbid obesity, strict control of caloric intake is required. Behavioral management, which removes or reduces conditions that increase the likelihood of misbehavior and increases those that foster good behavior, has been suggested as an appropriate technique for controlling abnormal behavior in PWS. Managing eating behavior is facilitated by imposing permanent restriction of access to food and by! establishment of regular meal times. When plans for the day include a non-routine event, such as a school outing, providing pre-planned lunches and setting clear limits for behavior can be useful in maintaining control. Programs designed to teach social skills may improve outcomes when patients with PWS participate in behavioral management programs aimed at weight control.

A recent Swiss study in young children with PWS and matched healthy controls showed that normal weight in PWS can only be achieved through external, e.g., parental, control. However, not only restriction of food but also a consistent style of upbringing in general improves weight control in PWS.

An intensive behavioral intervention program was successful in producing an average weight loss of 2.25 kg during 1 year of treatment in four children, aged 6 to 9 years, with PWS. Each child received a personalized low-calorie diet, underwent structured training in recognition of low and high-calorie foods, and participated in games focused on food. A program for parents was conducted concurrently.

**Other behavioral/psychological problems**

Abnormal behavior and psychological problems characteristic of PWS include skin-picking, daytime sleepiness, temper tantrums, stubborness, compulsions, and perseveration. In addition, a high incidence of affective disorders has been found among patients with PWS, and episodes of depression may be accompanied by psychotic
symptoms. Refractory behavioral or psychological problems generally require a comprehensive approach to management. In-patient treatment may be necessary if outpatient treatment is unsuccessful in modifying behavior.

A comprehensive behavior program that incorporates a structured living environment, behavior management techniques, group psychotherapy, and psychotropic medication has been effective in improving behavior problems in adolescents with PWS. Interestingly, patients participating in group therapy did not talk about their insatiable hunger but did discuss the clever ways in which they managed to steal food. In one group of 65 patients with PWS, about 75% required treatment with psychotropic medications; SSRIs, antipsychotics, mood stabilizers, and anxiolytics accounted for most medication use, and multiple medications were applied in some cases. Skin-picking generally did not improve during treatment with any psychotropic medication. In the experience of the authors, with proper behavioral and environmental management, only about 30% of adults and 15% of children with PWS require medication.

Skin-picking is the most prevalent form of self-injury among patients with PWS, with legs and head being the most frequently affected sites. Skin-picking was reported to have improved with fluoxetine (20-60 mg/day) in two patients with severe skin ulcers secondary to skin-picking; in one case, improvement was noted only after the dose was increased from 20 to 60 mg/day.

Risperidone, at doses from 0.5 to 3 mg/day, was found to be effective against aggressive behavior and temper outbursts in six adults and one adolescent with PWS who were living in a therapeutic setting and undergoing behavioral treatment.

In a 2-year controlled study, behavioral symptoms and symptom complexes were assessed in 54 children with PWS (aged 4 to 16 years; bone age <13 years and <15 years for girls and boys, respectively) before and after GH therapy (n = 35) with 1 mg/m²/day (~0.03 mg/kg/day) or customary treatment (controls, n = 19). In year 2, the controls crossed over to GH treatment. Compulsion and depression scores at 1 year were significantly (p <0.05) improved in the GH group, compared with baseline values, as were scores for skin-picking, although no between-group differences were found. After 2 years, the positive effect of GH therapy on depression was retained, with the major reduction in depressive symptoms occurring in those >11 years old. Surprisingly, from baseline to 2 years, symptoms of attention deficit/hyperactivity disorder increased significantly in those <11 years old, independent of treatment status. At no time, however, was behavioral deterioration reported. The observation that GH prevented a predictable deterioration in behavior in PWS children is intriguing, but further follow-up is required to confirm the effect and to rule out a possible ‘rebound’ after discontinuation of therapy. As there was no significant difference to the control group, it cannot be ruled out that the observed effects are due not to GH itself but to the increased attention and medical support accompanying GH therapy.

Cognitive deficits

Most, but not all, patients with PWS have mild-to-moderate mental retardation. In contrast to declines noted in patients with mental retardation associated with other genetic syndromes, cognitive function was found to be stable in a study of patients with PWS, as measured by a retrospective analysis of scores on repeated intelligence tests. IQ was not related to weight in this study.

Preliminary results suggest that individuals with PWS may have weaknesses in sequential processing. In a study in which cognitive function was evaluated in 21 patients with PWS, aged 13 to 46 years, using the Kaufman Assessment Battery for Children, significant differences among scale results were found on a repeated measures analysis of variance (F(2,40) = 27.44, p <0.001). As shown in Table 1, the patients performed best on achievement tests and subtests and worst on sequential processing. Further research is necessary, however, to confirm these findings.

Social cognition was identified as an area of cognitive weakness in a study of 11 adolescents, aged 10.1 to 17.1 years, with PWS. Participants were asked to interpret the intention of characters in stories involving lies, jokes, and broken promises. Few of them were able to identify lies or jokes or to differentiate between a promise broken intention-
TABLE 1
Mean K-ABC age equivalent scores and patterns of strength and weakness in 21 patients with Prader-Willi syndrome

<table>
<thead>
<tr>
<th>K-ABC Scale</th>
<th>Mean (SD)</th>
<th>Strength/Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential processing</td>
<td>5.29 (1.81)</td>
<td>W</td>
</tr>
<tr>
<td>Simultaneous processing</td>
<td>7.10 (2.05)</td>
<td>–</td>
</tr>
<tr>
<td>Achievement</td>
<td>8.24 (1.79)</td>
<td>S</td>
</tr>
<tr>
<td>Sequential processing subtests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand movements</td>
<td>4.62 (1.79)</td>
<td>W</td>
</tr>
<tr>
<td>Number recall</td>
<td>6.21 (2.85)</td>
<td>S</td>
</tr>
<tr>
<td>Word order</td>
<td>5.02 (1.27)</td>
<td>–</td>
</tr>
<tr>
<td>Simultaneous processing subtests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestalt closure</td>
<td>7.81 (3.01)</td>
<td>–</td>
</tr>
<tr>
<td>Triangles</td>
<td>6.85 (2.65)</td>
<td>–</td>
</tr>
<tr>
<td>Matrix analogies</td>
<td>7.54 (2.11)</td>
<td>–</td>
</tr>
<tr>
<td>Spatial memory</td>
<td>5.96 (2.16)</td>
<td>W</td>
</tr>
<tr>
<td>Photo series</td>
<td>7.36 (2.45)</td>
<td>–</td>
</tr>
<tr>
<td>Achievement subtests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>7.68 (2.09)</td>
<td>–</td>
</tr>
<tr>
<td>Reading/decoding</td>
<td>8.55 (2.16)</td>
<td>–</td>
</tr>
<tr>
<td>Reading/understanding</td>
<td>8.52 (2.09)</td>
<td>–</td>
</tr>
</tbody>
</table>

K-ABC = Kaufman Assessment Battery for Children.

ally or unintentionally, which points to difficulties in interpreting non-literal language and social situations\textsuperscript{31}. Speech and language disabilities may further interfere with social competence\textsuperscript{6,20,38,41}.

TEAM MANAGEMENT: A MULTIFACETED APPROACH TO A COMPLEX PROBLEM

PWS is a complex disorder that affects many organ systems and is associated with an evolving complex of clinical manifestations\textsuperscript{32-68}. Medical concerns are most prominent in patients with PWS during infancy and childhood\textsuperscript{68}, while behavioral manifestations assume increasing importance in affected adolescents and adults unless life-threatening obesity is present\textsuperscript{8}. Because PWS is associated with cognitive limitations as well as an uncorrectable deficit in appetite control combined with motor hypoactivity, lifelong supervision is required. Social service support, nutritional planning, and physical training programs are integral parts of overall treatment\textsuperscript{19,110,52}. The stimulation of motor activity in PWS may become increasingly important in the future, not only because hypoactivity is
the main cause of disturbed energy balance but also because a recent study showed that it is possible to motivate children with PWS to adhere to a simple physical training program. Such a program enhanced overall motor activity even in these mentally disabled patients.

Increased awareness about PWS and the availability of improved diagnostic tests have led to earlier diagnosis. Strict control of caloric intake, the use of GH in children with PWS and short stature, appropriate management of behavioral and psychological problems, social service support, and physical therapy have improved the life expectancy of patients with PWS, and survival into adulthood is now common.

Multidisciplinary management of all clinical manifestations of PWS is required to achieve optimal outcomes. None of the many problems associated with PWS can be managed with a single treatment. With comprehensive care by a multidisciplinary team that includes physicians, nurses, nutritionists, social workers, psychologists, physical therapists, and speech and language pathologists, weight can be controlled, the incidence of medical complications can be reduced, and cognitive and behavioral abnormalities can be managed. Speech and language evaluation and therapy may be required to improve communication skills. Moreover, the families caring for individuals with PWS need constant support. In this way, quality of life can be improved for both patients and their families.

The role of GH and sex steroid replacement therapy in adults with PWS is currently under investigation, and other new therapies for weight loss and stabilization may have some utility. Even during GH therapy, food intake and weight gain have to be monitored closely in patients with PWS. Screening for respiratory dysfunction seems mandatory, especially in infants with PWS and in adults with marked obesity. Patients with PWS should be evaluated for upper airway obstruction before initiation of treatment with GH. GH is contraindicated in patients with PWS who are severely obese or have severe respiratory impairment. Adult patients with PWS may also benefit from routine monitoring of cardiovascular risk factors, including lipid abnormalities, and bone density.

Individuals receiving GH therapy should also be monitored for aggravation of scoliosis and hypothyroidism and adequately treated. Improvements in management have created a new challenge for clinicians: the design of an optimal program of management for adults with PWS. The behavioral problems associated with PWS appear to intensify with age, although the cognitive defects do not worsen.

Patients with PWS may be susceptible to early development of certain medical problems associated with aging, including osteoporosis, sleep apnea, respiratory dysfunction, and cardiovascular disease, although two analyses suggest that the cardiovascular risk profile in obese patients with PWS differs from that of healthy obese patients. An unpublished national survey of 52 families of individuals with PWS aged 35 years and older, conducted by one of the authors (BYW), found that these individuals continue to struggle with behavioral problems and the consequences of being overweight, and they require ongoing management.

Patients with PWS, their families, and involved professionals can also benefit from organizations such as the Prader-Willi Syndrome Association (USA, Switzerland) and the International Prader-Willi Syndrome Organization. These organizations maintain web sites that provide a wide range of information about PWS, including treatment options and current research. Parents must be informed that all treatments for PWS should be administered under the supervision of one professional experienced in childhood PWS.

REFERENCES


JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM


57. Haqq AM, Farooqi IS, O’Rahilly S, Stadler DD, Rosenefeld RG, Pratt KL, LaFranchi SH, Purnell JQ. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. J Clin Endocrinol Metab 2003; 88: 174-178.


JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM