

# A Comprehensive Team Approach *to the Management of* Prader-Willi Syndrome

## Prader-Willi syndrome (PWS) is characterized by

infantile hypotonia; short stature; small hands and feet; increased body fat beginning in early childhood; decreased muscle mass; scoliosis; reduced resting energy expenditure (REE); reduced bone mineral density (BMD), which may lead to osteopenia and osteoporosis; hypogonadism; hypothalamic dysfunction; and a particular facial appearance. These clinical features are accompanied by hyperphagia, cognitive disabilities, and behavioral problems, including skin picking. In 70% of individuals, the syndrome is the phenotypic expression of a complex genetic disorder resulting from a paternally derived de novo deletion of the proximal long arm of chromosome 15 (at bands 15q11.2-15q13). Maternal disomy 15 (both 15s from the mother) is seen in about 25% of individuals with PWS and a methylation imprinting defect in the rest.<sup>1</sup> Prader-Willi syndrome and its sister syndrome, Angelman syndrome (an entirely different clinical syndrome), were the first examples in humans of genetic imprinting, or the differential expression of genetic information depending on the parent of origin. Prader-Willi syndrome is one of the most common conditions seen in genetics clinics worldwide and the most common genetic cause of marked obesity yet identified,<sup>2</sup> and its various clinical manifestations are major causes of morbidity and social limitations. Learning ability, speech and lan-

**Introduction.** *The treatment of children with Prader-Willi syndrome (PWS) represents a new challenge in the field of pediatric endocrinology. The handicaps and problems of affected children are manifold, more so than in any other typical disease of pediatric endocrinology, perhaps with the exception of craniopharyngioma. Therefore, management of children with PWS may be most successful with a team approach to comprehensive care.*

*We thank Pharmacia Corporation for organizing a workshop on such an approach in St. Julians, Malta, on April 24, 2001. This newsletter summarizes the proceedings of that workshop. The reader will notice that the development of a comprehensive professional team approach to PWS has only just begun. Much work remains to be done, primarily to define what, exactly, a "comprehensive team approach" to PWS means. For example, it appears necessary for one highly experienced specialist team member to assume leadership, to allow patients and their families to interact with one single professional. Further, growth hormone treatment has become a very important tool in the management of PWS. Nevertheless, it must be emphasized that without a comprehensive team approach, especially to restrict caloric intake and provide psychosocial support for families, children receiving growth hormone therapy will not lose weight, and the impact on their quality of life may remain relatively small.*

*Some centers have a great deal of experience and know-how in managing PWS. This know-how, however, is most often attributable to the experience of a single person. Through intensive study of the experience and strategies of such centers and individuals, a professional comprehensive team approach can be developed that will allow centers all over the world to offer optimum care to their patients with PWS.*

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guage, self-esteem, emotional stability, social perception, interpersonal functioning, and family dynamics, in addition to cognition and behavior, may all be adversely affected by PWS.

A panel of international experts on PWS was convened to share their clinical experience and to identify strategies for managing PWS. The panel agreed that, because PWS produces various adverse functional as well as metabolic effects, individuals with PWS require a variety of interventions to optimize their growth and development. These include growth hormone (GH) replacement; dietary management; physical and occupational therapy; speech, language, and learning disability services; behavior management; and family interaction, support, and care. Successful patient management requires a multidisciplinary team, which may include, among others, a PWS specialist and an endocrinologist—who may or may not be the same person—a nurse coordinator, a geneticist, a psychologist, and a dietitian. This newsletter describes such a team approach.

### GH EFFECTS ON PHYSICAL PARAMETERS IN PWS

Dysregulated GH secretion associated with deficient GH responses is the principal cause of short stature in the majority of children and adolescents with PWS. It is probably also an important contributor to the decreased muscle mass and osteopenia in patients with PWS, whereas hypogonadotropic hypogonadism is the probable primary cause of osteopenia and osteoporosis in these patients.<sup>3</sup> Evidence is mounting that a GH deficiency due to hypothalamic dysregulation may contribute not only to the abnormal growth pattern but also to the excess of body fat and the deficit of lean body mass in patients with PWS.<sup>4,5</sup> Growth hormone treatment of children with PWS normalizes linear growth,<sup>6-10</sup> promotes growth of lean body mass,<sup>7,8,11,12</sup> and decreases fat mass,<sup>7,8,11,12</sup> but its long-term benefits can be maintained only in conjunction with a multidisciplinary approach that empha-

sizes comprehensive care for the complex neurobehavioral and endocrine needs appropriate for the patient's age.

The role of GH as a component of the overall management of PWS has been studied extensively in the United States, Switzerland, and Sweden.

### American Experience

Parra and co-workers observed in 1973 that a deficient GH response to pharmacologic stimuli appeared to be related to the abnormal growth pattern in patients with PWS.<sup>13</sup> In 1987, Lee and colleagues reported for the first time that GH therapy led to significant increases in the linear growth rate of patients with PWS.<sup>6</sup> All the patients in their study initially had low serum levels of GH and insulin-like growth factor-I (IGF-I); during GH therapy, levels of IGF-I normalized. These results indicated that the low GH levels observed in these cases were not an artifact of obesity and supported the premise that the poor linear growth in patients with PWS might be caused by a true deficiency of GH.

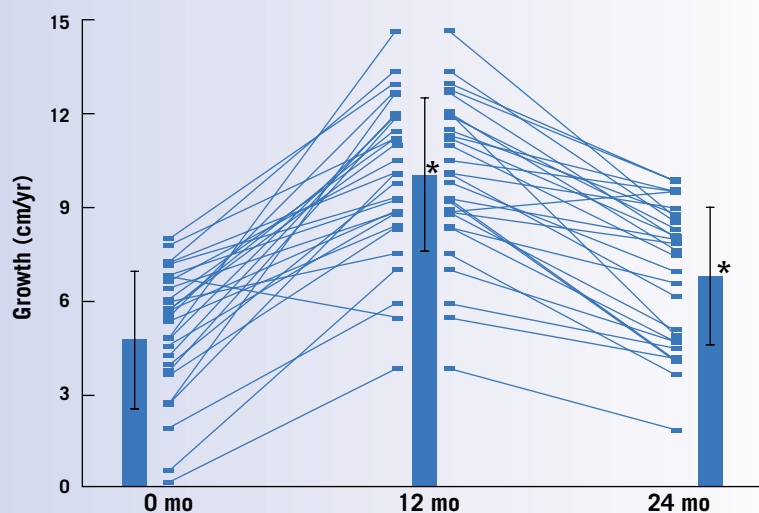
In 1993, Lee and collaborators reported the results of an uncontrolled trial of GH therapy in 12 obese children with PWS and associated chromosome 15 abnormalities.<sup>14</sup> All 12 children initially had low serum levels of GH, IGF-I, IGF-II, IGF binding protein-3 (IGFBP-3), and osteocalcin. These levels normalized and height velocity increased during GH therapy. Dual-energy x-ray absorptiometry (DEXA) at baseline revealed increased fat mass, normal (not weight-corrected) BMD, and very low lean body mass. Within 3 months of the patients' beginning GH therapy, DEXA revealed variable changes in fat mass and increased BMD and lean body mass, with redistribution of fat mass from the trunk to the thighs. The majority of parents reported improved behavior and appetite control.

The decreased GH secretion commonly seen in children with PWS had been considered by some to be an effect of obesity, but reduced GH secretion had also been found in non-obese children with

PWS. Angulo and colleagues studied 33 obese and 11 non-obese children with PWS to determine whether this suboptimal GH secretion was an artifact of obesity.<sup>15</sup> Spontaneous GH secretion was measured over 24 hours, and GH secretion was provoked by insulin, clonidine, and levodopa. Of the 44 subjects, 40—including 10 non-obese children—failed to respond to at least two of the stimuli, and 43 had reduced spontaneous 24-hour GH secretion. The investigators concluded that the GH deficiency seen in PWS is not a consequence of obesity but rather a significant contributor to the decreased growth velocity and increased adiposity typical of the syndrome.

In a controlled trial reported in 1999, Carrel and associates assessed the effects of GH therapy on growth, body composition, strength and agility, respiratory muscle function, REE, and fat utilization in 54 children with PWS, all of whom had low peak stimulated GH levels at baseline.<sup>7</sup> Thirty-five children received GH at a dose of 1 mg/m<sup>2</sup>/day and 19 were untreated. After 12 months, the GH-treated children showed significantly increased height velocity (**Figure 1**), decreased percentage of body fat, and improved physical strength, agility, and respiratory muscle function, although there was no significant increase in REE. The investigators concluded that GH therapy, in addition to its effect on growth and body composition, may have value in improving some physical disabilities experienced by children with PWS. After 24 months of GH therapy, patients had experienced sustained decreases in fat mass, increases in lean body mass, and improvements in physical strength and agility.<sup>8</sup> Height velocity remained significantly higher

**Individuals with PWS require a variety of interventions to optimize their growth and development.**



**Figure 1. Height velocity in patients with PWS treated with growth hormone (GH).** Thirty-five children received GH at a dose of 1 mg/m<sup>2</sup>/day for 24 months and 19 were untreated. After 12 months, the GH-treated children showed significantly increased height velocity. The growth rate slowed between 12 and 24 months, although height velocity remained significantly higher than at baseline (\**P*<0.01 compared with baseline [0 months]). (Reproduced with permission from Carrel AL, Myers SE, Whitman BY, Allen DB. Prader-Willi syndrome: the effect of growth hormone on childhood body composition. *Endocrinologist*. 2000;10(suppl 1):43S-49S.)

than at baseline (*P*<0.01), although the growth rate slowed between 12 and 24 months. To achieve these encouraging results, the investigators suggested, GH therapy should be started early; GH therapy started in middle to late childhood may not be capable of normalizing the percentage of body fat in patients with PWS.<sup>2</sup> However, GH therapy should not be started before the second anniversary, in the absence of conclusive data on GH therapy in infants. (In the United States, clinical trials of GH therapy in infants with PWS have been initiated in 2001.) At baseline, 70% of subjects had mild to moderate scoliosis on spine films.<sup>8</sup> During the first year of the study, no significant difference in scoliosis progression was seen between the GH-treated group (from a mean of 9.2° at baseline to 12.1°) and the control group (from 14.7° to 16.6°). During the second year, the mean change in curve measurement in the GH-treated group also was not significant.

Children with PWS should be evaluated and treated in a multidisciplinary clinic that is managed by a nurse coordinator and staffed by a physician PWS specialist, geneticist, psychologist, and dietitian. Ancillary resources should include support by neurology, physical therapy, social services, and educational services, as well as readily available facilities for measuring body composition (including whole-body DEXA) and studying exercise physi-

ology. The **Table** lists the components of the initial evaluation and testing. Follow-up visits are recommended at 6-month intervals for patients receiving GH therapy. In the majority of patients puberty will not occur, and gonadal steroid replacement therapy should be considered for them on the basis of clinical and DEXA findings.

### Swiss Experience

Disturbed satiation and energy expenditure remain the basic defects in PWS. Reduced muscle mass appears to be the consequence of decreased physical activity, which is probably caused by the central nervous system defects. Reduced muscle mass, in turn, is the cause of the decreased energy requirement. The benefit of GH therapy for children with PWS, according to Eiholzer's group, is an increase in lean body mass and a subsequent increase in REE. If energy intake is not increased, these alterations lead to a reduction of energy stores, mainly of body fat, and a dramatic change in phenotype (**Figure 2**). However, even though height and weight are normalized during GH treatment, children with PWS must maintain their energy intake at about 75% of the intake of healthy children to stabilize their weight for height. Such a reduction of food intake is possible only through close, strict parental supervision, and this is a major reason why families caring for

## Table. Recommended Components of the Initial Visit to a Multidisciplinary Prader-Willi Syndrome Clinic

### Evaluation

- Confirmation of diagnosis, genetic counseling
- Complete examination
- Dietary evaluation and counseling
- Physical therapy evaluation (developmental, neuromuscular)
- Psychological evaluation and recommendations
- Educational evaluation and recommendations
- Initial discussion of growth hormone therapy and approval process

### Testing

- DNA studies
- IGFBP-3, IGF-I, thyroid panel, lipid panel (other lab tests as clinically indicated)
- Screening for glucose intolerance if patient is obese (fasting glucose, glycated hemoglobin, oral glucose tolerance test, if indicated)
- Body composition analysis (DEXA, anthropometry, or other method)
- Psychological and/or educational testing
- Strength and endurance testing

DEXA=dual-energy x-ray absorptiometry; IGF-I=insulin-like growth factor-I; IGFBP-3=IGF binding protein-3.

a child with PWS need psychosocial support. Following is a short summary of the Swiss experience with GH therapy.

Eiholzer and l'Allemand described 23 children with genetically confirmed PWS and divided them into three groups: group 1 comprised young children who were not yet obese; group 2, prepubertal overweight children; and group 3, pubertal overweight children. All were treated with GH 24 U/m<sup>2</sup>/week (~0.037 mg/kg/day) for a median of 4 years (range, 1.5 to 5.5 years).<sup>9</sup> In group 1, weight and weight for height were lower than normal before treatment and continuously increased up to the normal range during treatment. In group 2, a dramatic height increase and drop in weight for height showed clearly



that these obese children had become not only taller but also slimmer with treatment. In group 3, however, the effect of GH on growth and weight was rather limited. The investigators concluded that if treatment is instituted early enough, growth becomes normal and height predictions reach the parental target height. This effect of exogenous GH on growth has so far been described only in children with GH deficiency.

Most importantly, although loss of fat mass, as determined by DEXA,<sup>12</sup> in the older children (group 3) was considerable with exogenous GH administration, fat mass was still in the upper-normal range (Figure 3). The influence of exogenous GH on muscle mass in PWS was found to be limited. Catch-up growth in muscle mass, as estimated by lean mass, was observed only during the first 6 months of therapy; thereafter, muscle mass increased in parallel with height. Therefore, it was deduced that muscle mass remained relatively decreased.

Improvement in body composition is the main goal in the treatment of children with PWS. According to the Swiss experience, the changes in body composition during GH therapy result from several therapeutic interventions. It is critical to maintain control of nutrient intake during GH treatment, in accordance with the reduced energy requirements in PWS. In children with PWS, energy requirements are about 50% below those of healthy children.<sup>17</sup> Growth hormone treatment does not change the feeling of satiety but increases the energy expenditure resulting from the increase of lean mass by an

estimated 25%, as shown by another Swiss study.<sup>18</sup> Weight for height and BMI decrease during GH treatment only if energy intake is not increased at the same time. It is therefore imperative that parents continue to keep patients' food consumption under control with the same rigidity as before the start of GH treatment.

Hypothesizing that increased muscle mass in infants may positively influence motor development, Eiholzer and colleagues used the Griffith test<sup>19</sup> to study psychomotor development in 10 young underweight children with PWS during the first year of GH treatment.<sup>20</sup> At baseline, the children were significantly more retarded on the "locomotor" and "hearing and speech" scales than on the other scales. During GH therapy, locomotor capabilities increased significantly, whereas hearing and speech remained unchanged. The treated children started walking unassisted at an average age of 24.1 months, about 4 to 6 months earlier than untreated children with PWS. Motor development thus seems to be improved by GH therapy.

In older children, improvement in physical performance is—in the opinion of the parents—the most important therapeutic effect of GH.<sup>21</sup> After 1 year of GH therapy, physical performance, as assessed by ergometry, significantly increased in peak and mean power in four prepubertal 7-year-old obese children. Such improvement in physical performance leads to an increase in activity, which, together with the disappearance of the obese phenotype, may relieve patients and their families of a major stigma that accompanies PWS, improving their quality of life.

The Swiss group was also able to show for the first time that insulin secretion in children with PWS is delayed and lower than that shown in otherwise normal, non-syndromal obese children and in children without PWS on GH therapy.<sup>22</sup> In addition, the increase in fasting insulin and insulin resistance seen in children with PWS during GH therapy is tran-



**Figure 2. A child with PWS before and 12 months after treatment with growth hormone (GH).** For GH therapy to increase lean body mass, reduce body fat, and stabilize weight for height, children with PWS must maintain their energy intake at about 75% that of healthy children.

sient.<sup>22</sup> Three years of GH therapy did not impair carbohydrate metabolism, but rather counteracted the potential GH-induced insulin resistance by decreasing fat mass and increasing lean mass. Since normal insulin sensitivity remains preserved, the investigators speculated that the primary mechanism for the development of diabetes in PWS is a reduced secretory capacity of pancreatic beta cells that persists despite GH administration.

According to the Swiss researchers, certain aspects of lipid metabolism differ in PWS and non-PWS obesity. In PWS, triglyceride levels are normal (although still correlated with abdominal obesity), but LDL cholesterol levels are elevated and HDL cholesterol levels are decreased.<sup>23</sup> These lipid levels normalize during GH therapy, but the changes are not associated with changes in body fat and probably are caused by the direct effects of GH deficiency and exogenous GH administration on cholesterol metabolism, as described in adult patients with GH deficiency.<sup>24</sup>

#### Swedish/Danish Experience

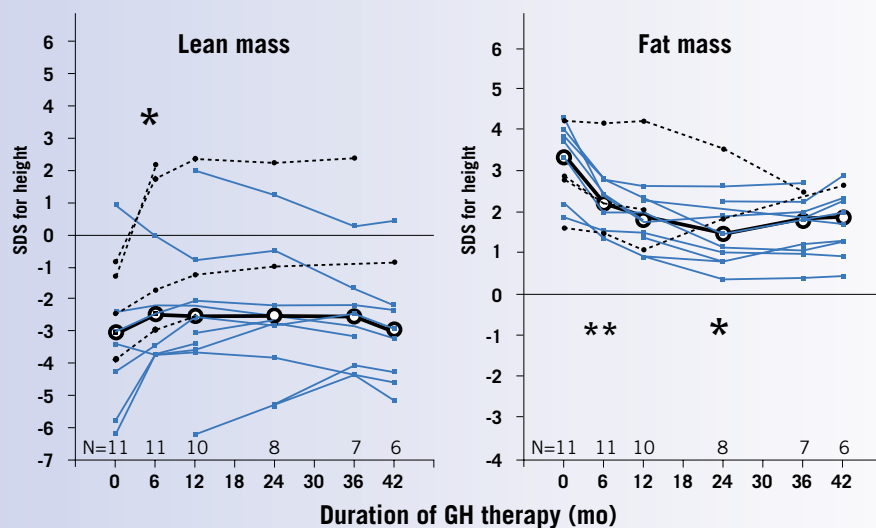
Despite the evidence from uncontrolled trials that GH therapy was beneficial in PWS, a number of pediatric endocrinologists continued to believe that the low lev-

***GH therapy should be started early, but not before the second anniversary, in the absence of conclusive data on GH therapy in infants.***

els of GH seen during provocation testing were a result of the characteristic obesity, and they were concerned that treatment with exogenous GH would negatively affect endogenous GH secretion. For this reason, the first randomized controlled study was conducted to assess the effect of GH therapy on growth, body composition, and other characteristics of the syndrome in prepubertal children. Lindgren and co-workers reported results of this study in 1997<sup>25</sup> and 1998<sup>26</sup> and 5-year results in 1999.<sup>10</sup>

After a 6-month evaluation period, patients with PWS between the ages of 3 and 12 years were randomized into group A (n=15), which received GH 0.1 IU/kg/day (0.033 mg/kg/day) for 2 years, or group B (n=12), which received no treatment for the first year but GH 0.2 IU/kg/day (0.066 mg/kg/day) during the second year. After 2 years, all children stopped GH therapy for 6 months and then restarted GH therapy at a dose of 0.1 IU/kg/day (0.033 mg/kg/day). The 6-month GH-free interval was included to prove that the effects of GH therapy were reversible, and the low and high doses were included to compare their effects.

Before GH therapy, all patients had low blood levels of GH, as shown by frequent samples over 24 hours, as well as low IGF-I and insulin levels. During the first months of the study, IGF-I levels increased rapidly to supranormal values in group A (GH therapy) but remained essentially unchanged in group B (no treatment). With respect to growth, height velocity standard deviation scores (SDS) increased from -1.9 to 6.0 during the first year of GH therapy in group A, followed by a lower rate of increase during the second year. In group B, height velocity SDS decreased slightly during the first year of the study (no treatment) but increased rapidly from -1.4 to 10.1 in the second year of the study (GH therapy). When GH therapy was stopped for 6 months, height velocity declined dramatically in both groups; height SDS followed a similar pattern. Growth hormone thera-



**Figure 3. Body composition measured by DEXA in 16 children with PWS.** Body composition is expressed as the height-related standard deviation score and compared with reference values for a Dutch population older than 4 years or taller than 100 cm.<sup>16</sup> The graphs show medians (○, thick black lines) and individual courses of young underweight (n=4; ■, blue lines), prepubertal overweight (n=8; ■, blue lines), and pubertal children with PWS (n=4; ●, dotted lines) treated with growth hormone (GH). Significant differences vs baseline at 6, 24, and 42 months (\* $P<0.05$ , \*\* $P<0.01$  [Wilcoxon test]). (Reproduced with permission from Eiholzer U, Bachmann S, l'Allemand D. Is there growth hormone deficiency in Prader-Willi syndrome? Six arguments to support the presence of hypothalamic growth hormone deficiency in Prader-Willi Syndrome. *Horm Res.* 2000;53(suppl 3):44-52.)

py reduced the percentage of body fat from 40% to 30% and increased the muscle area of the thigh by 33%, as measured by computerized tomography; isometric muscle strength also increased. In addition, parents reported that GH therapy seemed to have psychological and behavioral benefits, which were reversed after treatment was stopped. However, cognitive functions (IQ) did not change, nor did the parents report any change in appetite. The authors stressed that strict control of caloric intake had to be maintained during GH treatment to obtain the desired reduction in body fat.

Patients with PWS are known to easily fall asleep when inactive. This has been ascribed to the impaired breathing secondary to obesity (the pickwickian syndrome). However, Lindgren et al<sup>27</sup> showed that PWS patients have a markedly reduced CO<sub>2</sub> response, ventilation, and central inspiratory drive, which improved during GH therapy. The reduced CO<sub>2</sub> response points to a hitherto unknown chemoreceptor dysfunction.

Five-year follow-up data on 18 of the children were published in 1999.<sup>10</sup> Following resumption of GH therapy after the 6-month discontinuation, height SDS again increased (Figure 4). Body mass index SDS stabilized at 1.7 for group A (n=9) and 2.5 for group B (n=9). In 16

children, levels of fasting insulin, glucose, and the A<sub>1c</sub> fraction of glycosylated hemoglobin remained within normal ranges. The remaining two children developed non-insulin-dependent diabetes mellitus following a period of rapid weight gain, but glucose homeostasis returned to normal when GH was discontinued. Unpublished 7-year follow-up data show that mean height has normalized with prolonged treatment.

## CLINICAL MANAGEMENT OF PWS-ASSOCIATED BEHAVIORS

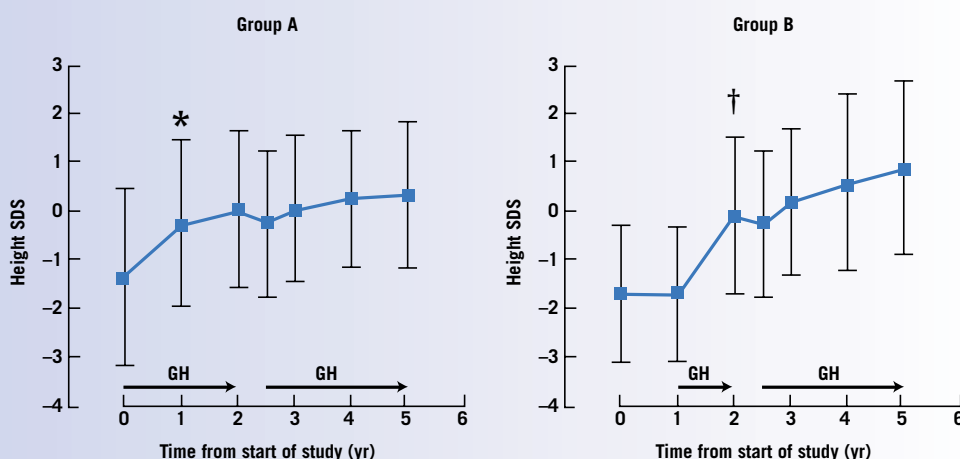
The hypothalamus plays an important role in regulating appetite, sensitivity to pain, body temperature, and the day/night cycle, all of which may be abnormal in patients with PWS. The hypothalamus also plays a role in regulating emotions and memory, and children with PWS typically experience emotional excess and short-term memory impairment. The behavioral sequelae of these abnormalities, however, are not manifested clinically until chronologic adolescence. From birth until the age of 3 years, the pre-

**When GH therapy was stopped for 6 months, height velocity declined dramatically.**

dominant problem among patients with PWS is extreme hypotonia, a component of which is, paradoxically, difficulty eating. At about the age of 3 years, delayed speech and emerging hyperphagia predominate, but the younger child with PWS is typically described as happy, affectionate, and cooperative.<sup>28</sup> By adolescence, behavioral problems characteristically have evolved as a major issue for patients with PWS and their families. Adolescents with PWS have been described as stubborn, impulsive, manipulative, irritable, mood-labile, angry, perseverative, egocentric, demanding, and prone to rage episodes when frustrated.

accompanied by depression, obsessions, or even frank psychoses, and they ultimately are responsible for the inability of adults with PWS to succeed in alternative living and work placements. Interestingly, many of the characteristic behaviors of patients with PWS, including cognitive rigidity, hoarding behavior, impaired judgment, denial of deficits, inability to self-monitor behavior, and interpersonal conflicts, are also seen in patients with traumatic brain damage. In patients with PWS, however, the brain damage is genetic and, unlike traumatic brain damage, appears to affect the entire brain. Prader-Willi syndrome may thus be characterized

lems, learning disability associated with short-term memory and sequencing deficits,<sup>29</sup> and failure to develop the ability to apply knowledge in new situations (metacognitive ability). Most patients with PWS score between 60 and 80 on IQ tests, and at least some have IQ scores in the 90s or somewhat higher. Functional aptitude, however, is entirely independent of test scores and appears to be related more to the degree of cognitive rigidity. Impaired metacognitive ability prevents patients with PWS from utilizing their typically extensive compendium of facts in a practical or productive manner. Difficulty with sequencing and language deficits underlie most of the behavioral problems and the inability to change some behaviors. Sequencing difficulty extends beyond simple numerical applications and includes an inability to recognize cause-and-effect sequences. This particular problem necessitates an entirely different approach to traditional behavior management, since patients with PWS fail to link punishment or reward with an antecedent behavior. Many patients with PWS who frequently exhibit problem behaviors are able to alter these behaviors when environmental changes are instituted. These changes require creativity, hard work, and, often, many months before a behavior is altered, and some environmental and family situations are unalterable. It is particularly difficult when parents disagree about the management approach. Children with PWS who have the worst behavior in terms of depression and anxiety come from families in which parents report the highest level of conflict over child rearing. Although this is also true for normal children, children with PWS do not have the flexibility seen in normal children. Therefore, family therapy is recommended as soon as the diagnosis of PWS is made in an infant or young child.



**Figure 4. Height velocity standard deviation scores (SDS) in patients with PWS treated with different regimens of growth hormone (GH) over 30 months.** Group A received GH at a dose of 0.1 IU/kg/day (0.033 mg/kg/day) for 2 years. Group B was untreated for the first year and then received GH at a dose of 0.2 IU/kg/day (0.066 mg/kg/day) during the second year. After 2 years, all children stopped GH therapy for 6 months and then restarted GH therapy at a dose of 0.1 IU/kg/day (0.033 mg/kg/day). Values are means ± SD. (\* $P < 0.001$  compared with baseline; † $P < 0.03$  compared with baseline.) (Reproduced with permission from Lindgren AC, Ritzén EM. Five years of growth hormone treatment in children with Prader-Willi syndrome. The Swedish National Growth Hormone Advisory Group. *Acta Paediatr Suppl.* 1999;433:109-111.

Transitioning from one activity to another becomes increasingly difficult, and there is a tendency to confuse day with night. Thus, the centrally driven food-related behavior constellation, although dramatic, is just one of many neurobehavioral abnormalities characterizing this disorder, and the food behavior often is the easiest to manage.

These behavioral traits are frequently

as a pervasive developmental neurobehavioral syndrome whose behavioral manifestations reflect a distributed central nervous system dysfunction that has yet to be fully described either anatomically or biochemically.

In addition to behavioral problems, four cognitive difficulties have been identified in patients with PWS: global mental retardation, language processing prob-

**Family therapy is recommended when the diagnosis of PWS is made.**



For many patients with PWS, problem behaviors are resistant to most attempts at behavioral management, and pharmacologic interventions are often considered when this becomes clear. Unfortunately, psychopharmacologic agents frequently worsen problem behaviors in these individuals. A survey of parents of children with PWS conducted between 1989 and 1993 revealed that almost every available psychotropic agent had been prescribed to manage behavioral problems.<sup>30,31</sup> Most agents either were ineffective or increased the occurrence of targeted symptoms; only three—haloperidol, thioridazine, and fluoxetine—were effective.<sup>32</sup> More recently, it has been found that all serotonin-specific reuptake inhibitors seem to have a nonspecific behavior-stabilizing effect, characterized by fewer outbursts, a marked reduction in irritability, and less perseveration, but with no specific antidepressant effect.<sup>33</sup> Other psychotropic drugs, such as the antipsychotic agent olanzapine and the anticonvulsant agent divalproex sodium, may have an effect.<sup>33</sup> It must be emphasized, however, that any single agent may produce a dramatically beneficial response in some patients with PWS and a dramatically adverse response in others, and many patients with PWS have idiosyncratic reactions to psychotropic drugs. Those with PWS require only one fourth to one half the standard dose of a psychotropic drug to achieve a benefit; increasing the dose to “normal” often results in toxicity and a return of the problem behavior.<sup>33</sup> In general, psychotropic medication should be used only when all other interventions, including behavioral modification and environmental changes, have failed.

It should also be noted that appetite-suppressing medications have been ineffective in controlling food-seeking behavior and overeating.<sup>1</sup> Pharmacologic agents, including the amphetamines and agents that block the absorption of fat, which are often effective in the so-called normal obese population, do not appear to alter the brain signals, or perhaps

peripheral signals, that drive patients with PWS to seek food and overeat. Until a medication is discovered that can accomplish this goal, good management depends entirely on environmental control, protection against overeating, and an understanding caregiver who recognizes that the constant feeling of hunger experienced by these patients underlies some of their irritability.

With regard to the effect of GH therapy on PWS behavior in the setting of behavioral difficulties and refractoriness to psychopharmacologic agents, surveys of parents indicate that some behaviors improve and none deteriorate.<sup>28,34</sup> Since the behavior of children with PWS tends to deteriorate over time, the absence of deterioration is, in fact, a positive outcome. Specific behavioral benefits of GH therapy, as reported anecdotally by parents, included increased energy, increased activity without the need for encouragement, improved personal hygiene, less “annoying” behavior, increased assumption of responsibility, and less perseveration.<sup>28,34</sup> In addition, attention span and compliance seemed to improve and anxiety, depression, and obsessive thoughts decreased, although there was no impact on obsessive-compulsive behavior or improvement in school performance. Growth hormone therapy also produced positive effects on physical appearance, usually within 3 to 6 months of patients’ starting treatment. Appearance of the hands, feet, and trunk normalized in all GH recipients, and appearance of the head normalized in 81%. Such changes may positively affect patients’ social interaction. Furthermore, 97% of patients had more energy and 83% spontaneously increased their level of physical activity without parental prodding.

### **IMPROVING QUALITY OF LIFE IN PATIENTS WITH PWS: DIET, EXERCISE, AND LIFESTYLE CHANGES**

Surveys performed in the United Kingdom in 1989 and 1999 have provided useful information about the impact of

lifestyle changes on PWS. From the standpoint of diet, two distinct phases of PWS are apparent: initial failure to thrive and subsequent obesity.

Failure to thrive results primarily from hypotonia, which makes sucking difficult during infancy, and nasogastric tube feeding may be necessary for as long as 2 months to meet energy requirements. Signs of poor feeding in infants with PWS include changes in the voice or cry, coughing while swallowing, excessive drooling, frequent vomiting, constipation, respiratory infections, irritability during feeding, slow intake, and poor weight gain. For infants who are able to suck, specially designed nipples can reduce the energy expenditure. Early weaning to soft food will reduce energy requirements; introduction of solids is accompanied by a lessening of appetite for milk.<sup>35</sup> However, some 33% of older infants with PWS are unable to eat soft food normally acceptable at 1 year, and children with PWS typically lag far behind children without PWS in their transition to solid food, with 42% of children with PWS unable to chew some solid foods at the age of 5 years.<sup>36</sup>

The change from failure to thrive to hyperphagia generally occurs between 2 and 4 years; there seems to be a recent shift toward the younger age. Despite their reduced energy requirement, these children are obsessed with food and engage in food seeking and food stealing. Overeating may be due to the prolonged eating drive that results from their disturbed feelings of satiety.<sup>37</sup> The vast majority of parents of children with PWS have attempted to control their children’s weight, but continuous dietary compliance is difficult. Severe caloric restriction for short periods at home or for longer periods in the hospital setting is normally helpful, but some families still feel that no intervention will help.

Increased physical activity can increase energy expenditure, promote negative energy balance, raise the post-exercise metabolic rate, build muscle mass, pre-

vent osteoporosis, improve scoliosis, and enhance the overall sense of well-being. However, very few patients with PWS seem to participate in a structured exercise program. Aerobic exercise, toning and strengthening, flexing and stretching, and formal physiotherapy are all useful for patients with PWS. Activities they may find acceptable include bicycling, skating, jumping on a trampoline, dancing, and ball playing.

Lifestyle changes that can be implemented certainly include control of food-seeking and food-stealing behaviors but also must encompass social integration and independence. Specific environmental controls designed to limit hyperphagia include locking places where food is stored, restricting access to money or credit cards, and prohibiting participation in food preparation. Unfortunately, many of these impositions and limitations may actually discourage social integration and independence.

## SUMMARY AND CONCLUSION

Because of its many physical and behavioral manifestations, PWS should be managed in a multidisciplinary setting that emphasizes comprehensive care. Clinical trials confirm that GH treatment of children with PWS normalizes linear growth, promotes an increase in lean body mass, and decreases fat mass. However, the long-term benefits of GH can be maintained only in conjunction with dietary control and counseling, physical therapy, and psychological and educational evaluation and support.

***The long-term benefits of GH can be maintained only in conjunction with dietary control, physical therapy, and psychological and educational evaluation and support.***

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