

Prader-Willi syndrome: Update on treatment by growth hormone

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Prader-Willi syndrome (PWS), described in 1956¹, is characterized by an early phase of severe neonatal hypotonia with feeding difficulties and poor weight gain, followed by a second phase marked by intense bulimia leading to morbid obesity, growth retardation, frequent hypogonadism, learning difficulties and behavior problems as well as signs of dysmorphism and acromicria. The diagnosis is above all clinical and should be established as early as the neonatal period in the presence of any severe, unexplained hypotonia. Holm's criteria, described in 1993², are very helpful in diagnosis and are also instructive concerning the clinical features, classified by age and importance (major and minor criteria). On a genetic level, PWS was the first condition in which the mechanism of parental genomic imprinting was revealed in man³⁻⁶. Genetic confirmation of the diagnosis is based on demonstration of an abnormality of the methylation pattern, due either to a microdeletion (65%), to maternal disomy (35%) or to a mutation of the genetic imprinting center (1 to 5%).

Growth retardation is not a constant sign in PWS and its frequency is poorly evaluated. It is nevertheless a cardinal feature of the syndrome, whose pathophysiology is now better understood.

The major questions which are raised today concerning treatment with growth hormone (GH) are three in number:

1. Is there a growth hormone deficiency in patients with PWS?
2. What effects does the treatment have (on growth, body composition, carbohydrate and lipid metabolism...) and what are its potential risks?
3. What are the indications of GH and what treatment modalities and surveillance are required?

SPONTANEOUS GROWTH

Two important German teams have established growth and weight curves for patients with Prader-Willi syndrome^{7,8}. The former were published by Wollmann in 1998 (315 patients) and the latter by Hauffa in 2000.

At birth there is no intra-uterine growth retardation but height is slightly below the mean (-0.23 SDS in boys and

-0.53 SDS in girls). Nevertheless, these were retrospective studies and gestational age was not very accurately assessed. Weight shows greater abnormality than height (-0.87 SDS in boys and -1.17 SDS in girls).

Adult height is about 159.0 ± 5.3 cm for men and 148.6 ± 5.5 cm for women, which is below -2 SDS for both sexes. Obesity is very frequent and severe if no early and effective treatment has been proposed, with a body mass index (BMI) of 31.9 ± 0.4 kg/m² in men and 35.2 ± 0.29 kg/m² in women⁹.

Another important auxological criterion of the syndrome is the presence of acromicria (small hands and feet) which can be measured and compared with specific curves.

INVESTIGATION OF GROWTH HORMONE SECRETION IN CHILDREN WITH PWS

For many years, pediatric endocrinologists believed that the low serum GH levels in these patients were related to their obesity. We now know that GH levels are often low in common obesity but levels of insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) are normal or even elevated, indicating increased sensitivity to GH.

In patients with PWS, several arguments confirm the existence of true GH deficiency whose prevalence is difficult to define (40 to 50%):

1. Growth retardation is present in 50 to 80% of cases.
2. Levels of spontaneous GH secretion and secretion after pharmacological stimulation are decreased¹⁰⁻¹².
3. And are associated with severely diminished levels of IGF-I and/or IGFBP-3 in almost 100% of cases¹³.
4. GH levels after stimulation by GH-releasing factor (GRF) are generally decreased (20%).
5. There is a hypothalamic syndrome¹⁴.
6. MRI reveals pituitary hypoplasia in about 60% of cases¹⁵⁻¹⁷.

The GH deficiency is probably part of the complex hypothalamic syndrome found in these patients and its pathophysiology is still poorly known. Necdin, a protein in-

involved in the control of neuronal proliferation and encoded by an imprinted gene located in the PWS region, is very strongly expressed at the level of the hypothalamus but its involvement in the hypothalamic syndrome is as yet undefined^{18,19}. Various features of PWS, such as central hypogonadism, neonatal hypotonia, disturbances of thermal regulation, absence of satiety, daytime sleepiness and the sleep apnea syndrome are connected with the hypothalamic syndrome¹⁴.

Acromicria and the increased fat mass associated with decreased lean mass may be related to GH deficiency, which may also make a non-negligible contribution to hypotonia. Possibly the most cogent argument in favor of the existence of a GH deficiency in children with PWS is that the hormone replacement markedly improves or even corrects the various symptoms, that is, growth, acromicria and body composition, and normalizes IGF-I and IGFBP-3 levels.

RESULTS OF GROWTH HORMONE TREATMENT IN CHILDREN WITH PWS

A number of studies have now been published^{17,20-30} making it possible to sum up the different effects of the treatment, on growth as well as on other aspects such as body composition, lipid and carbohydrate metabolism, muscular strength, pulmonary function, behavioral disturbances and cognitive functions.

Effects on growth

All short and medium-term studies confirm the very marked acceleration of growth velocity (GV) in children who had a decreased GV before treatment, with a mean gain in GV of 3 to 4 SDS. The effect decreases with time but GV is maintained above 0 SD for the duration of treatment. Predicted final height is improved. Very few studies have reported final height under treatment. In our retrospective study¹⁷, three girls have reached final height (-3.5 ± 0.75 SDS) but the main benefit seems to relate to the BMI, which is markedly lower than that of patients who had not received GH (33 ± 5 vs 27 ± 1 kg/m²).

The long-term effect is little known but studies are currently being carried out.

Here we must insist on the need for close surveillance of spinal posture in children receiving GH, as scoliosis is more frequent in children with PWS. The development or aggravation of scoliosis is not a direct effect of GH treatment but is related to the acceleration of growth velocity under treatment.

Effects on body composition

A decrease in fat mass is observed, mainly abdominal^{20-22,24-26,29,30}, and an increase of muscle mass. These effects are observed in the BMI and the waist/hip ratio but can be more precisely analyzed by dual energy X-ray absorptiometry (DEXA), a method which permits analysis not only of fat mass and total lean mass, but also of its distri-

bution (trunk/limbs) as well as of bone mineral content and bone mineral density during a single examination. Even in the youngest PWS children (under the age of 4 years), who are not obese or who may be just overweight, or even underweight, fat mass is high and lean mass is decreased before treatment and these abnormalities are corrected with GH²⁹. This abnormality of body composition can usually be at least partially explained by the GH deficiency since similar abnormalities are observed in GH-deficient patients without PWS and are improved by the treatment. Concerning GH-deficient patients without PWS, data on body composition have been studied mainly in adolescents and adults^{31,32}.

DEXA cannot assess the intra- and extra-abdominal distribution of the fat mass, which must be analyzed by a CT section passing through the middle of the intervertebral disk L4-L5³¹. This is an important point to make since it is the intra-abdominal (visceral) fat mass which is associated with increased cardiovascular risk.

Data on leptin must be mentioned here; leptin is elevated in patients with PWS but is less elevated, for an identical BMI, than in other obese children, probably because of their lower muscle mass^{33,34}.

All the results concerning body composition have been obtained in studies where particular attention was paid to dietary management and healthy living. This overall approach to management of the child and the active participation of the family in partnership with the care team are fundamental elements in optimizing treatment.

Effects on carbohydrate metabolism

This effect caused considerable concern among pediatric endocrinologists, on the one hand because GH treatment is known to increase fasting insulin levels in GH-deficient patients and on the other hand because of the morbid obesity which is frequent in patients with PWS and their risk of diabetes^{35,36}. A recent paper established the prevalence of diabetes in more than 20,000 children who had been treated with GH, for whatever cause³⁷. Non-insulin-dependent diabetes mellitus (NIDDM) is a complication of PWS but the severity of obesity as well as family history are major factors in its development. These patients thus require systematic and particularly close surveillance: oral glucose tolerance test (OGTT) before treatment, fasting glucose and insulin, and HbA1C levels at least once a year and at shorter intervals during GH treatment.

However, it is extremely interesting to be able to report here that in the 3 months following the beginning of treatment patients treated with GH have an increase of fasting insulin levels with no glucose anomaly and that hyperinsulinemia decreases secondarily under treatment³⁸. The secondary decrease in hyperinsulinemia, which is not observed in non-PWS patients treated with GH, may possibly be due to increased lean mass and decreased abdominal fat mass, as these two factors which are markedly improved

in these patients increase insulin sensitivity and thus lead to a decrease in insulin secretion. These recent findings are somewhat reassuring but do not dispense with the need for close surveillance.

Effects on lipid metabolism

Lipid metabolism has been little studied in patients with PWS but the data are comparable with those of the literature concerning non-PWS GH-deficient patients, with a decrease of total cholesterol and LDL-C associated with an increase of HDL-C, while triglycerides tend to decrease³⁹.

Other effects

Pulmonary function

Patients with PWS have reduced vital capacity^{24,25} which is probably due to muscular hypotonia but may also be linked with central effects. Two studies have reported significantly improved pulmonary function with increased strength of the inspiratory and expiratory muscles^{24,25,40}.

Muscular strength and agility

In the only study^{24,25} in which muscular strength and agility were analyzed using objective measurements, GH treatment led to improvement in running speed, in jumping (broad jump) and abdominal and arm muscle strength.

In the other studies, subjective improvement was observed and families reported better spontaneous mobility and readiness to participate in physical activity. This is extremely important in the overall management of the disease⁴¹.

Energy expenditure

Resting energy expenditure (REE), measured by indirect calorimetry, is significantly lower in PWS patients and GH treatment tends to increase it^{24,25}. In a study we performed, we demonstrated that REE is correlated with IGF-I levels. It should also be noted that with GH treatment the respiratory quotient decreases from 0.81 ± 0.07 to 0.77 ± 0.05 the first year and to 0.75 ± 0.06 the second year^{24,25}.

Bone mineralization

We have found no mention of altered bone mineral density (BMD) in the literature on PWS children. Nevertheless, GH treatment significantly increases femoral BMD and total BMD^{24,25} from 0.89 ± 0.08 to 0.92 ± 0.11 at 12 months and 0.94 ± 0.11 at 24 months.

Effects on behavior

Scandinavian authors^{20,21} have reported interesting findings by families whose children have received GH treatment: the children seem to have more stable behavior during treatment, reverting to their former behavior when it is discontinued.

We must insist on the fact that the phenotype of children with PWS is extremely variable whatever the genetic form of the disorder, suggesting that as in other genetic conditions epigenetic factors –modifying genes and the environment– play a role. This is a further justification of pluridisciplinary management, optimized and harmonized around a unique patient and his or her family and adapted according to the child's age.

The place of growth hormone treatment

It is the first time that a medical treatment (apart from psychotropic medications) is offered these patients and it is treatment which has a significant impact on the major characteristics of the disorder: GH treatment increases growth velocity and height, modifies body composition and with appropriate dietary management prevents obesity, improves physical and respiratory performances and through them the quality of life, and it may prevent the long-term cardiovascular and metabolic consequences (hypercholesterolemia, diabetes). The impact on behavior requires further analysis. The possibility of providing the PWS child with an effective treatment is motivating for the physicians, the whole care team and of course the families.

The interest of this treatment is multiple. Besides the principal effects we have described, it requires specific prescription and follow-up by a pediatric endocrinologist who will thus be motivated and will be the necessary coordinating physician for the child and his or her family, working in close collaboration with the treating physician (pediatrician or general practitioner) and the various medical, paramedical, social and educational personnel involved. Thanks to growth hormone treatment, we believe these patients will now benefit from better follow-up and their families will receive greater support.

Indications, initiation and follow-up of GH treatment in PWS

The growth hormone commercialized by Pharmacia Laboratoires received its European marketing license in 2000 for the treatment of PWS and neglected disorders. In Europe this is a "syndromal" indication concerning children presenting PWS confirmed by genetic findings with the aim of increasing growth velocity and improving body composition. The North American license relates only to the effects on growth.

There is no lower age limit, nor auxological limit (the children are not necessarily small) nor any need to demonstrate growth hormone deficiency.

The recommended dose is the same as that used in the treatment of GH deficiencies: 0.7 IU/kg/week (0.23 mg/kg/week).

Dietary management must be initiated at the same time.

So today, in Europe, children with PWS can be treated with GH even if they do not have GH deficiency or growth retardation.

Recommendations proposed by the author

Recommendations will very certainly be formulated in the near future and a consensus is needed.

Ideally, the child would be observed without treatment for 6 months to 1 year. It seems logical, but not mandatory, to carry out:

1. Investigation of the somatotrophic axis (1 provocative test, 1 measurement of IGF-I and IGFBP-3).
2. Bone age measurement once a year.
3. Study of body composition by anthropometric measurements of height, weight, BMI and waist/hip ratio, and by DEXA once a year.
4. Systematic examination for scoliosis at each visit and orthopedic follow-up if necessary. X-rays are obtained at the beginning of treatment and as required afterwards.
5. Evaluation of the parameters monitored in any treatment by GH: thyroid hormones, TSH (particularly as a hypothalamic deficiency is found in 30 % of cases), calcium and phosphorus levels.
6. Investigation of carbohydrate and lipid metabolism once a year: HbA1C, fasting glucose and insulin levels, OGTT at the beginning of treatment, cholesterol, total cholesterol, HDL-C, LDL-C and triglycerides.
7. Dietary, psychological/psychiatric and neurological follow-up, speech therapy and physical therapy of course form an integral part of management.
8. If the child is obese, I propose calculating the GH dose on the basis of the theoretical weight for height in order to avoid over-dosing these patients, and increasing the dose progressively if the IGF-I levels are not above 0 SDS.

CONCLUSION

GH treatment for PWS is a major advance both in the management of these children and in our knowledge of the pathophysiology of the syndrome, and it also stimulates the motivation of the care team and the families. Nevertheless, today many questions still remain unanswered. Studies must be continued in these children with particular emphasis on the long-term outcome. We also already need to address the issue of GH treatment in adults with PWS and to prepare adult endocrinologists for the care for these patients by taking advantage of the collaborative efforts now being developed concerning adolescents with severe GH deficiency persisting after growth is completed.

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