Consensus document on Growth Hormone (GH) treatment in adults with Prader-Willi syndrome

Growth Hormone treatment in patients without PWS

Treatment with growth hormone (GH) started in the late 1950s, and in the early decades of treatment, only children received GH. Assessment of efficacy was clinical and consisted of measurement of height and body proportions. Potential side effects, such as diabetes and cancer, were projected from the clinical picture of GH excess (acromegaly). In the late 1980s recombinant human GH (rhGH) became available and the interest in GH's important metabolic effects intensified. The typical clinical picture of severe Growth Hormone Deficiency (GHD) in adults is well-defined and includes abnormal body composition, fatigue, decreased physical activity, adverse cardiovascular risk profile, and reduced quality of life (QoL). Since 1990, adults with severe GHD according to specified diagnostic criteria have been treated with GH and several studies have documented that GH improves body composition, cardiovascular risk factors and QoL with few side effects.

Growth Hormone treatment in adults with PWS

Testing for Growth Hormone Deficiency in PWS

A dysfunction of the hypothalamus is generally accepted in Prader-Willi syndrome. Most GH stimulating tests measures the secretion of GH from the pituitary, which can lead to falsely normal GH responses in patients with GH deficiency of hypothalamic origin such as, patients with PWS. In addition, the increased amount of adipose tissue in PWS has been proposed as a confounder to an impaired response. In studies reporting results from GH testing, profound GHD in adults with PWS, defined according to existing diagnostic criteria, was demonstrated in 0 to more than 50%.

Among the GH dependent peptides insulin like growth factor I (IGF-I) is the most frequently used marker of GH secretion. The concentration of IGF-I is stable over 24-hours and is used for titrating of the GH dose. In PWS, the majority of adults have low concentrations of IGF-I but IGF-I levels are known to be affected by nutritional status, presence of sex steroid deficiency, differences in GH molecular size or defects in the GH receptor, and these issues as well as spontaneous GH secretion are other factors for GHD not completely examined in PWS. In summary, available studies suggest that insufficient GH secretion is intrinsic in PWS and it can be argued whether GH stimulation tests

are clinically indicated. However, IGF-I should be analysed as part of the evaluation for GHD.

As GH treatment in adults with PWS is only registered in a few countries, GH treatment is usually discontinued when final adult height is reached and a new evaluation of GH secretion performed.

Growth Hormone treatment in adults with PWS

Adults with PWS share similarities with non-PWS adults with GHD in particular as regards body composition with reduced lean body mass (LBM) and increased fat mass (FM), and it is therefore likely that GH treatment would have beneficial effects in adults with PWS similar to those seen in non-PWS adults.

A meta-analysis of eight studies (including 134 adults with PWS) on GH treatment in adults with PWS found that in all studies GH treatment improved body composition with an increase in LBM and a reduction in total FM, subcutaneous and visceral fat. Furthermore, a long-term double blind placebo-controlled trial observed beneficial effects on regional fat mass. The effects were maintained in an extended open label phase of the study. Similar changes in body composition after GH treatment have previously been described in a smaller randomized placebo-controlled study, as well as in open labelled studies. Two studies reported observational data in six and 15 adults treated with GH for 5 and 15 years respectively, also found sustained and maintained positive effects on body composition. BMI did not change during GH treatment, but BMI does not accurately reflect body composition due to the increased amount of body fat and GH is not a weight reducing medication.

Inactivity is common in PWS and a measurable improvement in physical activity would be a clinically relevant consequence of the improvement in body composition. Treadmill and accelerometers have been used showing improved tests results during GH treatment trials. An indirect increase in muscle function was shown by an increase in peak expiratory flow (PEF) and other studies reported improvement in the questions on physical activity included in QoL questionnaires. It is an issue to find the right method to monitor physical activity and obtaining maximal physical capacity will need encouragement. On the other hand, portable devices are being developed and might also be useful in this group of patients.

The effect of GH on quality of life (QoL) in adults with PWS has been evaluated in four studies using different questionnaires and they all showed significant improvement from baseline and in one study a clear impairment was seen in physical and social status as well as in over-all functioning when GH treatment was discontinued. Assessment of QoL in adults with PWS is difficult because of

the cognitive deficits, behavioural and psychiatric problems. In addition, development of appropriate tests/questionnaires to be used for evaluation of QoL in PWS is needed. Only one study has evaluated the effect of GH treatment on neuropsychological tests in adults with PWS. In this study a test battery of eleven sub-tests suitable for adults with cognitive deficits were applied and it was found that some of the cognitive and the motor performance tests improved during GH treatment.

It is not known whether low BMD in PWS is caused by impaired GH secretion, low levels of sex-steroids, low muscular activity or low intake of calcium and D-vitamin or a combination of all of them. In a recent study, GH treatment during 2-3 years did not increase BMD, probably because of the relatively short period of treatment. In addition, the patients had not systematically received sex hormone replacement. Bone formation markers increased with GH treatment, whereas resorption markers were unchanged. The results indicate a multi-factorial cause for low BMD and not solely a consequence of impaired GH secretion.

Unfavourable levels of blood lipids increase the risk of cardiovascular disease, but in PWS this is observed less often than would be expected related to the frequently present obesity. However, beneficial effects on blood lipids and cardiovascular function have been reported in both short- and long-term GH treatment.

In the period from mid- to late teens until 6-7 years after achievement of adult height, known as the transition period, discontinuation of GH in young adults with GHD has been shown to result in recurrence of the symptoms of GHD which improved after GH treatment was resumed.

Side effects

Overall, GH treatment is generally safe and well tolerated. The prevalence of diabetes mellitus has been estimated to be 25% in adults with PWS, despite of them having less insulin resistance, and lower fasting insulin levels than expected when compared to weight matched controls. One of the main physiological effects of GH is an increase in glucose, insulin and insulin resistance. However, only a small increase in blood glucose, trends towards an increase in insulin and insulin resistance were reported in the studies of GH treatment in adults with PWS. On the individual level some patients might have predispositions for diabetes, and it is important to carefully monitor glucose metabolism during GH treatment and overdosing with GH should be avoided. Other side effects reported in studies of adults with PWS are transient mild peripheral oedema, muscle pain and headache, similar to reports from other patient groups treated with GH.

Growth Hormone doses and duration of Growth Hormone treatment

GH doses between 0.2 and 1.6 mg have been used in studies in adults with PWS. In the individual patients a GH dose resulting in IGF-I values between 0 to +2 SD scores for age-matched controls is recommended. Treatment should be continued as long as benefits outweigh the risks.

Comments from the CSAB

GH treatment offers an opportunity to relieve some of the adverse effects of PWS but it is not mandatory for life. The CSAB acknowledge the positive effects of GH and support this treatment in adults with PWS.

The goal of GH replacement in adults with PWS is to optimise metabolism and body composition as well as physical fitness and QoL. In the new generation of young adults treated with GH during childhood the goal is to maintain the positive effects of GH treatment already obtained.

The major contraindications for GH treatment (active cancer, proliferative retinopathy, severe obesity and uncontrolled diabetes) must be considered before starting GH treatment, also in PWS.

Some additional issues should be considered in adults with PWS. The incidence of *central apnoea* and *obstructive apnoea* is high in PWS and GH treatment can theoretically lead to worsening of the obstructive apnea through growth of lymphoid tissue. However, an increase in sleep apnea during GH treatment has not been reported in adults with PWS. *Scoliosis* occurs in 30-80% in PWS, and GH treatment has not been shown to affect neither incidence nor rate of progression. Therefore, scoliosis is not a contraindication. Clinically relevant *central adrenal failure* in PWS is rare, but of note GH accelerates the shift from active cortisol to the inactive cortisone and adrenal insufficiency and hydrocortisone treatment should be evaluated when clinically indicated. *Central hypothyroidism* occurs in PWS and as GH increases the peripheral conversion of T4 to T3, thyroid function should be followed regularly during GH treatment. *Hypogonadism* is seen in the majority of adults with PWS. In a patient receiving GH treatment it is important to remember that oestrogen has a negative and testosterone a positive effect on IGF-I generation and if treatment with sex steroids are introduced GH doses might need to be changed.

Future

From a basic science perspective, we need to understand the nature of the reduced activity of the GH-IGF axis in PWS. From a clinical science perspective measures for evaluation and monitoring of as well physical performance as QoL needs to be developed and validated. GH is currently administered by subcutaneous injections in the evening which might be inconvenient for some patients. Several formulations with long-acting GH for injections once weekly are developed and the efficacy and safety in early phase studies and short-term studies have been shown to be comparable to treatment with one daily subcutaneous injection of GH. However, long-term data are needed before the role of long-acting GH can be decided. When they are obtained long-term GH preparations might be more convenient for many patients with PWS and result in a better compliance and adherence to the GH therapy.

In summary

- GH treatment improves body composition, physical fitness and quality of life
- Major contraindications to GH treatment are severe obesity, uncontrolled diabetes mellitus, proliferative retinopathy and active cancer
- Cognitive impairment and scoliosis are not contraindications to GH treatment
- GH treatment is safe but glucose metabolism, especially in patients with predisposition for diabetes, must be evaluated continuously. Likewise changes in respiration and other hormones
- Treatment should be continued as long as benefits outweigh the risks.

IPWSO 2019