

# **An Update on the Indications of Growth Hormone Treatment under Hospital Authority in Hong Kong (revised in June 2019)**

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Growth hormone (GH) has been used to treat patients with GH deficiency in Hong Kong since 1978. In 1998, the Hospital Authority extended the use of GH in children with Turner syndrome and chronic renal failure before transplantation. Two additional indications Prader Willi syndrome and short stature homeobox-containing gene disorders were approved in 2012. Besides being used for growth promotion, it also aims at improving body composition for patients with PWS. The objective of this short communication is to highlight the recommendations of GH treatment for children and adolescents with these conditions in Hong Kong. Interested colleagues should refer to the original articles for details.

## **Growth hormone deficiency**

Children suspected of GH deficiency should have clinical and auxological assessments together with exclusion of other systemic causes of short stature. Insulin-like growth factor -1 (IGF-1) could be measured but low concentration is also found in children with malnutrition, hypothyroidism and liver disease. GH provocative tests can be performed with pharmacological agents such as glucagon, arginine, L-dopa and insulin. A peak GH level of less than 7-10 ug/L in two stimulation tests is considered abnormal but the cut-off level is assay-dependent.<sup>1,2</sup> In the presence of pathological causes such as brain tumour and multiple pituitary hormone deficiency, one abnormal provocative test is sufficient for the diagnosis. Diagnosis of GH deficiency without GH provocative test in patients with abnormal auxological assessment, hypothalamic-pituitary defect and deficiency of at least one additional pituitary hormone is suggested recently. There is also suggestion that GH deficiency due to congenital hypopituitarism can be diagnosed without formal GH provocative test in a newborn with hypoglycaemia who has GH level  $\leq 5$  ug/L, classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk) and deficiency of at least one additional pituitary hormone.<sup>3</sup> Sex hormone priming may be considered in girls aged  $>11.5$  and boys aged  $>13$  years old who are still in prepubertal stage or have only early signs of puberty.<sup>4</sup> It may also be considered in prepubertal girls aged  $>10$  years and boys aged  $>11$  years old with adult height prognosis within  $-2$  SD of the population mean.<sup>3</sup> Magnetic resonance imaging (MRI) of the brain and hypothalamic-pituitary region should be performed in any child diagnosed with GH deficiency.<sup>2</sup>

## **Turner syndrome**

Turner syndrome (TS) is characterized by short stature, dysmorphism, cardiac, renal anomalies and primary hypogonadism in phenotypic females. Most Turner patients do not have GH deficiency essentially but there is GH or IGF-1 resistance.

Studies have demonstrated an average final height gain was around 5 to 8 cm over a treatment period ranging from 5.5 to 7.6 years although response to treatment can be variable. GH should be considered as soon as growth failure (decreasing height centiles) is noted. Oxandrolone at a dose of 0.05 mg/kg/day; maximum 2.5 mg/day may be given in conjunction with GH in girls who are older than 8-9 years of age and have extreme short stature to optimize height gain. Virilization and liver function should be monitored.<sup>5</sup>

### **Prader Willi syndrome**

Prader Willi syndrome (PWS) is characterized by severe neonatal hypotonia, short stature, hyperphagia after infancy leading to morbid obesity, learning disabilities and endocrine problems including GH deficiency, hypothyroidism, hypogonadism and possibly adrenal insufficiency. It is caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13.<sup>6</sup> Studies including those on the long-term use of GH have demonstrated improvement in height, body composition, lean body mass and bone density without significant adverse side effects.

PWS patients are at risk of developing obstructive sleep apnoea (OSA) and central hypoventilation during sleep. Unexpected deaths occur in PWS patients with or without GH treatment. There are concerns GH may exacerbate upper airway obstruction and increase the risk of death in PWS patients. Hence, it is recommended to start with a lower dose. Insulin-like growth factor-1 (IGF-1) level should be monitored at least twice yearly and maintained within two standard deviations (SD) above the mean because it may worsen OSA.<sup>6</sup> Sleep study and ear, nose and throat (ENT) evaluation should be performed before and within 6 months after starting GH. Treatment should be instituted for sleep disorder and delay of GH therapy considered in severe OSA until improvement is demonstrated.<sup>6</sup> GH is contraindicated in patients with uncontrolled morbid obesity (body weight greater than 200% of ideal body weight for height) or severe respiratory impairment.<sup>8</sup>

### **Short stature homeobox-containing (SHOX) gene disorders**

The SHOX gene encodes a homeodomain transcription factor responsible for long bone growth and is located in the pseudoautosomal regions at the distal ends of the X and Y chromosomes.<sup>9</sup> Normal growth requires two functional copies of the gene. Haploinsufficiency of one copy of the SHOX gene is responsible for growth deficit in patients with Turner Syndrome (TS), 50-90% of patients with Leri-Weill dyschondrosteosis (LWD) and 2-15% of patients with idiopathic short stature. The phenotypes of individuals with SHOX gene disorders can be highly variable, ranging from short stature without obvious dysmorphism to severe mesomelic skeletal dysplasia (shortening of the forearms and lower legs). The mean adult height was -2.2 SDS.<sup>10</sup>

Studies have shown that the long-term effectiveness of GH in this disorder is similar to that in Turner patients.<sup>11</sup> GH is recommended in those with abnormal slow growth velocity and height less than -2.32 SDS (1<sup>st</sup> percentile) for age and sex.<sup>8</sup>

### **Chronic renal insufficiency before renal transplantation**

Growth failure is common in patients with chronic kidney disease (CKD). Factors including protein-calorie malnutrition, acid-base disturbances, hyperparathyroidism, glucocorticoid treatment, derangements in the GH-IGF axis and GH insensitivity contribute to growth failure. Despite management and interventions of these factors, poor growth persists in some children with CKD.

Studies have shown GH may increase the adult height by approximately 7-11 cm in children with CKD.<sup>12</sup> GH treatment is recommended when the creatinine clearance is less than 60 ml/min/1.73m<sup>2</sup> and body height was less than -1.88 SDS (3<sup>rd</sup> centile) for age and sex which persists beyond three months despite treatment of nutritional deficiencies and metabolic abnormalities. It is suggested to perform X-ray hips before initiating GH treatment and to stop GH in the presence of active renal osteodystrophy (hyperparathyroidism) as slipped capital femoral epiphysis is more common in patients with CKD. Recommendation on the duration and time of initiating GH in children after renal transplant requires further study.

### **Side effects of Growth Hormone**

Pseudotumour cerebri (benign intracranial hypertension) may develop but usually resolves after stopping GH. Slipped capital femoral epiphysis and worsening of existing scoliosis tend to occur in rapidly growing children and may require surgical correction. Continuation of GH treatment is recommended in general.<sup>13</sup> GH may induce carbohydrate intolerance in children with compromised insulin secretion. Hence checking fasting plasma glucose and HbA1c before and during GH therapy especially for those at risk including Turner syndrome, PWS syndrome and obese patients is suggested.<sup>14</sup>

There are concerns about a possible role of GH treatment in cancer pathogenesis. Data from several observational studies have suggested that for patients with isolated growth failure, GH treatment does not increase the risk for cancers compared with the age-matched general population. Studies of childhood cancer survivors noted little or no increased risk for secondary malignancy. For patients with other non-cancer diagnosis that required GH treatment like Turner syndrome or hypopituitarism without cancer, there was a modest increase in cancer risk, primarily due to an excess of bone or bladder cancer based on small number for each site.<sup>15</sup>

Nevertheless, it is recommended to start GH treatment one year after the completion of tumor treatment with no further evidence of tumour recurrence or growth. Monitoring of IGF-1 level is recommended to ensure that it is maintained within two standard deviation above the mean.<sup>13</sup>

### Summary of the indications and dosages of growth hormone treatment

Indications	Growth hormone dosage	
	mg/kg/day (IU/kg/week)	Dose / m <sup>2</sup>
Growth hormone deficiency	0.025-0.05 mg/kg/day (0.5-1 IU/kg/week)	4.5-7.5 mg/m <sup>2</sup> /week
Turner syndrome	0.045-0.05 mg/kg/day (1 IU/kg/week)	4.5-9.5 mg/m <sup>2</sup> /week
SHOX gene disorders	0.045-0.05 mg/kg/day (1 IU/kg/week)	4.5-9.5 mg/m <sup>2</sup> /week
Chronic renal insufficiency before renal transplantation	0.045-0.05 mg/kg/day (1 IU/kg/week)	28-30 IU/m <sup>2</sup> /week 4.5-9.5 mg/m <sup>2</sup> /week
Prader Willi syndrome	<i>Non-mature skeleton:</i> start with a lower dose and increase gradually to 0.035 mg/kg/day; maximum 2.7 mg/day <i>Mature skeleton:</i> 0.005 mg/kg/day (0.12 IU/kg/week)	<i>Non-mature skeleton:</i> start with a lower dose at 0.23-0.33 mg/m <sup>2</sup> /day (5-7 IU/m <sup>2</sup> /week) and increase gradually to 1 mg/m <sup>2</sup> /day (21 IU/m <sup>2</sup> /week); maximum 2.7 mg/day (8 IU/day)

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