Growth Hormone Therapy for Adults with Prader-Willi Syndrome

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Prader-Willi Syndrome: Background

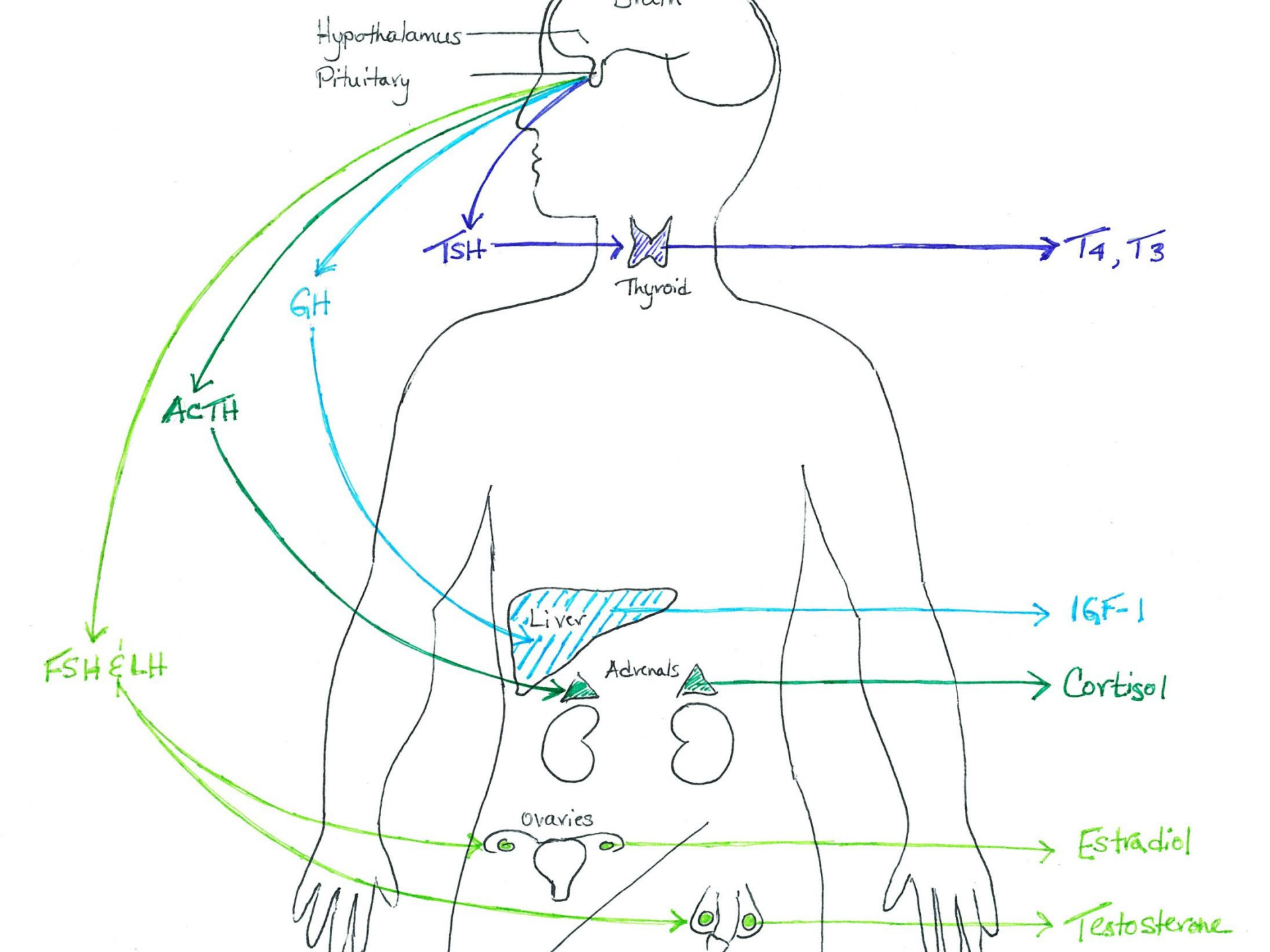
- Prevalence 1/10,000-1/30,000, sporadic
- Lack of expression of genes on paternally inherited long arm of chromosome 15: 15q11.2-q13
- Genomic imprinting
  - 70% deletion of paternal long arm of chromosome 15
  - 25% maternal UPD
  - 5% imprinting defect

PWS: Clinical features

- Infancy
  - Small for gestational age
  - Hypotonia with weak suck and poor feedings
  - Respiratory difficulty
  - Males with cryptorchidism
- Childhood
  - Hyperphagia and obesity
  - Short stature
  - Developmental delays, cognitive disability
  - Behavioral issues

PWS: Hypothalamic Dysfunction

- Non-endocrine
  - Hyperphagia, temperature instability, high pain threshold, sleep disordered breathing
- Secondary pituitary insufficiency
  - Short stature/growth failure
  - Hypogonadism
  - Cortisol deficiency (central, rare)
  - Hypothyroidism (central)


Brain
Hypothalamus
Pituitary
TSH
Thyroid
T4, T3
GH
ACTH
FSH & LH
Liver
IGF-1
Adrenals
Cortisol
Ovaries
Estradiol
Testosterone

Diagnosis of Growth Hormone Deficiency (GHD)in Pediatric PWS

- Growth failure is cardinal feature
- Prevalence 40-100%
- Low IGF-1 levels
- Decreased GH secretion on provocative testing
  - L-DOPA/Inderal, Clonidine, Glucagon, Arginine
  - Peak stimulated GH values <10 ng/dL
- Supported by clinical short stature despite obesity, abnormal body composition, increased incidence of osteoporosis

Endocrine Benefits of hGH Therapy in Pediatric PWS

- Improved linear growth
- Improved bone mineral density
- Improved body composition
- Improved lipid profile
- Possible improvement in cognition
- Benefits are seen in non-GHD PWS patients
- hGH treatment has FDA approval for pediatric patients with PWS, regardless of whether GHD

hGH

- Synthetic
- Somatropin, no generic
  - Brands: Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Zomacton, Skytrofa
- Administered SQ daily, though Skytrofa weekly
  - Home self/parent administration
  - Pen devices with fine, short pen needles
  - Virtually painless administration

Adult PWS Health Issues

- Higher mortality rate
- Up to half attributable to cardiopulmonary causes
- Complex interplay of hypotonia, hyperphagia, pituitary deficiencies, and behavioral challenges
- Increased fat mass, decreased muscle mass
- Morbid obesity, hypertension, hypercholesterolemia, Type II Diabetes Mellitus

Adult hGH therapy in PWS

- Role less clearly defined
- Prevalence of GHD 0-38%, worse stimulated GH response in UPD subtypes
- Several studies show benefit in body composition, bone density, exercise capacity, quality of life
- Ongoing treatment needed to maintain benefits
- May require provocative testing for insurance approval
- Dosing: 0.1-0.2 mg/day, titrate up by 0.1-0.2 mg increments to maintain IGF-1 in normal range

Metabolic health profile in young adults with Prader–Willi syndrome: results of a 2-year randomized, placebo-controlled, crossover GH trial

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- 27 adults (height growth complete)
- Mean age 17.2 years
- All completed childhood hGH treatment
- Treated with hGH 0.67 mg/m2 or placebo for one year, then crossed over for one year
- Dexa scans for body composition
- During placebo: increase in mean fat mass (4.1 kg) and decrease in lean body mass (0.9 kg)
- During hGH: decrease in mean fat mass (2.9 kg) and increase in lean body mass (1.5 kg)
- No adverse affects attributable to hGH

Visceral adipose tissue increases shortly after the cessation of GH therapy in adults with Prader-Willi syndrome

Mikiko Koizumi1), 2), Shinobu Ida1), Yasuko Shoji1), Yukiko Nishimoto3), Yuri Etani1) and Masanobu Kawai1), 4)

endocrj.EJ18-0107

- Measuring changes in Visceral Adipose Tissue (VAT) and Subcutaneous Adipose Tissue (SAT)
- DEXA and Abdominal CT
- Baseline before discontinuing hGH, then 6 or 12 months after cessation of hGH
- 7 adults (3 male, 4 female)
- All treated in childhood of hGH starting at mean age 4.1 years
- hGH was discontinued at mean age of 18.9 years after tapering down to 0.1 mg/kg/wk
- At 6 and 12 months, significant increase in fat mass
- Abdominal CT showed increase in VAT rather than SAT
- IGF-1 declines slightly, LDL cholesterol increased

Growth Hormone Treatment for Adults With Prader-Willi Syndrome: A Meta-Analysis

Anna G. W. Rosenberg,Caroline G. B. Passone,Karlijn Pellikaan,Durval Damiani,Aart J. van der Lely, Michel Polak,Wanderley M. Bernardo, and Laura C. G. de Graaff

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- Meta-analysis included 9 random controlled and 20 non-random controlled studies
- At least 6 months of hGH treatment
- Improvement in body composition
  - Increase in lean body mass, average 1.95 kg
  - Decrease in mean fat mass, 2.23%

Potential Side Effects

- Sleep apnea (OSA)
- Peripheral Edema
- Glucose Intolerance, Type II Diabetes Mellitus
- Neoplasm (theoretical risk)
- High doses can cause acromegalic changes, hypertension, cardiomyopathy, skin thickening, enlargement of organs

Adult hGH dosing and monitoring

- May require GH stimulation testing after discontinuing pediatric treatment: glucagon or macimorelin
- Starting dose of 0.1-0.2 mg SQ daily
- Titrate upwards to keep IGF-1 in normal range
- Annual monitoring of IGF-1, GlycoHbA1c
- Consider baseline sleep study and addressing OSA
- Absolute contra-indications: uncontrolled Type II Diabetes, uncontrolled sleep apnea, active neoplasm

Conclusion

- Global community of PWS experts has advocated for GH therapy for adults with PWS
- Höybye C, Holland AJ, Driscoll DJ; Clinical and Scientific Advisory Board of The International Prader-Willi Syndrome Organisation. Time for a general approval of growth hormone treatment in adults with Prader-Willi syndrome. Orphanet J Rare Dis. 2021;16(1):69.
- Duration of treatment should be individualized, continuing as long as the benefits out-weigh the side effects.