Growth Hormone Treatment in Prader-Willi Syndrome

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Photo source: http://www.clpmag.com/news/18982-a-ceaseless-hunger-the-prader-willi-syndrome

Objectives

- Explore the metabolic effects of Growth Hormone (GH) on Prader-WillI syndrome(PWS)
- Identify possible causes and sign/symptoms of PWS
- Evaluate the current research on the effectiveness of GH
- Analyze the administration of GH as a treatment option for PWS

Introduction

- Initially described by Prader, Willi and Labhart in 1956.[1]
- Prader-Willi syndrome (PWS) is a congenital disease
- Effects one in 10,000 to 15,000 children.[2]

Signs

- Early Failure To Thrive(FTT)
- Hypotonia
- Poor sucking
- Almond-shaped eyes,
- Narrow bi-frontal skull
- Scoliosis
- Small hands and feet in comparison to child's body
- Increased fat mass
- Hypogonadism
- Short stature[3]

Photo source : http://www.aafp.org/afp/2005/0901/p827.html

Symptoms

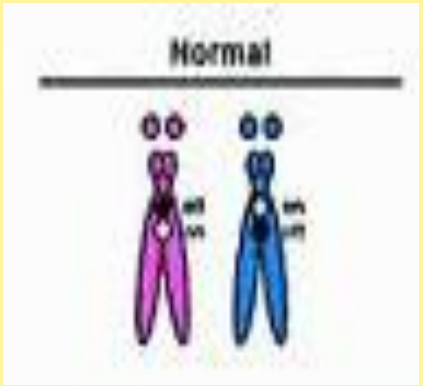
- Delayed motor development skills
- Compromised respiratory function
- Intense craving for food and hyperphagia
- Uncontrollable weight gain
- Abnormal body composition
- Reduced muscle tone and lean body mass
- Morbid obesity

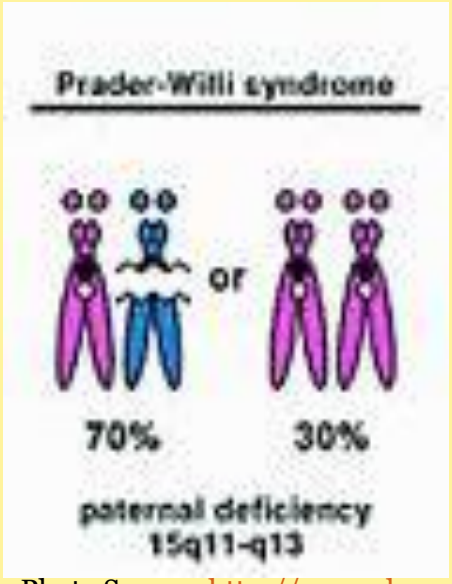
Symptoms

- Decreased Growth Hormone (GH)
- Decreased IGF-I secretion
- Diminished bone mineral density
- Reduced mental ability
- Sleep disorder
- Temperature instability

Main Causes of Genetic Defect

- Lack of genetic expression on chromosome 15q11-q13
- Deletion
- Maternal disomy
- Translocation





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Growth Hormone (GH)

An approved medication by Food and Drug Administration for long term treatment of children with growth failure due to PWS in the United States.[6]

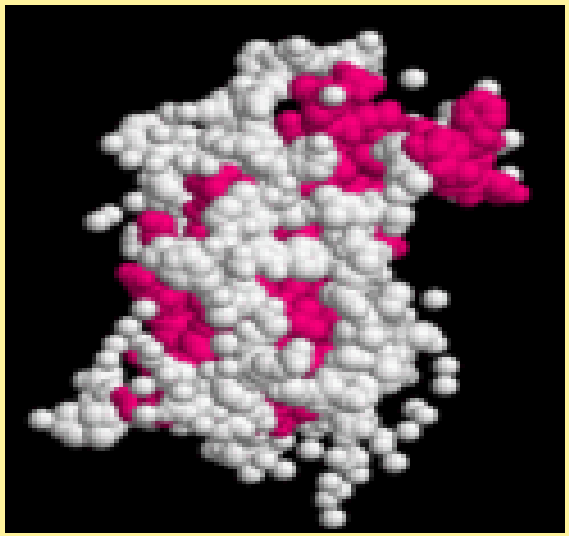

Photo Source:
http://en.wikipedia.org/wiki/Growth_hormone

Growth Hormone (GH)[5]

- Produced by the pituitary gland
- Fuels childhood growth
- Helps maintain tissues and organs system
- Stimulates production of insulin-like growth factor I (IGF-I)
- Glucose sparing effect
- Protein synthesis
- Lipolysis

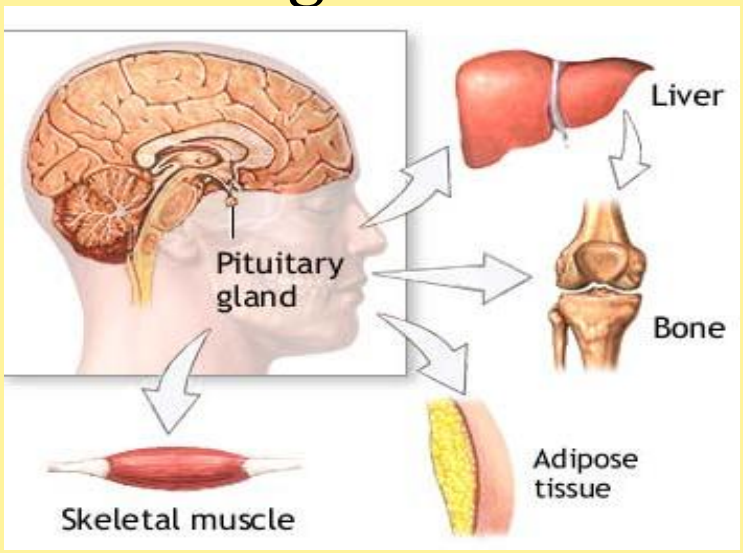

Photo Source: http://www.umm.edu/presentations/100146.htm

The Early Treatment Cohort Study

Objective: To compare similar aged children who have or have not received long term GH treatment in order to assess the impact of GH therapy begun early in life

Population: 48 children

- 21 children, (6 to 9 years) treated with 1mg/m^2/d
- 27 children (5-9 years) prior to treatment

Methods: Comparisons were made for percent body fat, lean body mass, carbohydrate/lipid metabolism, and motor strength

The Early Treatment Cohort Study

Results: children treated with GH early in life

- ↓ 8.5% body fat
- ↓ 31mg/dl lower LDL

- ↑ 14mg/dl higher HDL
- ↑ 16 cm in height

Conclusion: GH treatment begun prior to 2 years of age, improves body composition, motor function, height, and lipid profiles.[1]

The Dutch Multicenter Prospective Trial[4]

- **Objective:** To investigate the effects of long term treatment on body composition
- **Population:** 55 pre-pubertal children, age 5.9 years
- **Method:** Children received a dose of 0.5mg/m²/d
- Dose adjustment
- Maximum dose 1mg/m²/d
- Dietary counseling
- Continuous physical therapy

The Dutch Multicenter Prospective Trial

Results

- ↓ Fat %, LDL cholesterol, BMI
- ↑ LBM, height , head circumference

No significant change

Total cholesterol, HDL , blood pressure, hand and foot length, arm span, insulin dependent Diabetes Mellitus.

Conclusion:

Long term administration of a standard dose of 1mg/m²/d has beneficial effects specially on height if administered several years before puberty.

A Retrospective Study in France[8]

Objective: Compared changes in serum IGF-I, IGF binding protein 3 (IGFBP-3), IGF-I to IGFBP-3 molar ratio and growth velocity

Population: 33 children with PWS and 591 with GH deficiency (GHD)

Method:

- Mean initial dose 0.9 and 1 mg/m2/d in the PWS and GHD groups, respectively.
- Serum IGF-I and IGFBP-3 measured at 0, 6, 12, and 24 months

A Retrospective Study in France

Results:

↑ Serum IGF-I and IGFBP-3 in the PWS group

Conclusion: Positive association between higher growth velocity and sensitivity to GH in PWS children

US Adult Prader-Willi Syndrome Study[6]

Objective: Evaluate the effectiveness and safety of GH in adults

Population: 30 adults between the ages of 17 and 49 years.

Method: 12 month open label multicenter trial

- 6 months dose optimization period-dose of 0.2mg/d
- 6 months stable treatment periods
- Constant mean does of 0.6mg/d
- Dose adjustment for water retention and edema
- Qualitative data -physical strength

US Adult Prader-Willi Syndrome Study

Results:

↓ %fat ~43 to 40

↑ LBM

↑ T3

No significant change

HbA1c

Normal fasting BG

TSH

Conclusion:

GH treatment has beneficial effects on percent fat and LBM and it normalizes IGF-I without glucose impairment.[6]

The Scandinavian Multicenter Placebo Control, Double Blind Trial

Objective

To explore the effects of one year GH treatment on different fat compositions and LBM

Population

46 Adults (16-50 years)

Method

- 0.3 or 0.4 mg/d for initial 4 weeks phase
- 0.6 or 0.8mg/d for the next 11 months
- Consistent caloric intake and exercise [2]

The Scandinavian Multicenter Placebo Control, Double Blind Trial

Results:

Subcutaneous & visceral fat ↓

Total fat ↓

LDL cholesterol ↓

IGF-I level ↑

LBM ↑

No significant change

Total cholesterol

HDL

TG

fasting glucose/ insulin

BMI

Conclusion:

GH treatment for 12 months can decrease total and regional fat mass and improve LBM in adults.[2]

Bottom Line

- Diet and lifestyle modification
- Strict physical activity regimen
- Length of treatment----Short term studies as compared with the long term studies

Bottom Line

- Treatment dosage
- Assess if the benefits outweigh the side effects
- PWS is a relatively young disease with not enough data

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