Prader-Willi syndrome-different patients, different attitude

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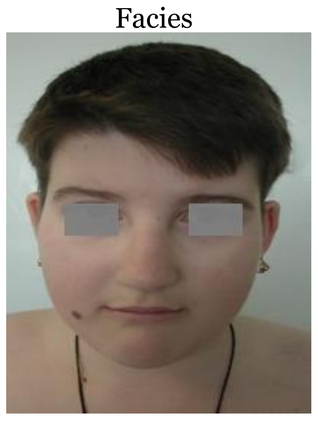
Introduction

- Prader-Willi Syndrome (PWS) is a multisystemic genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 characterized by
  - dysmorphic features, hypotonia, mental retardation, behavioral abnormalities, hyperphagia with progressive obesity and endocrine dysfunctions as hypogonadism and GH deficiency (GHD) (1)
- Risk factors for mortality in PWS include severe obesity, obstructive sleep apnea, upper respiratory tract infections (URI), aspiration, and tonsilor/adenoid hypertrophy
- The major cause of morbidity and mortality is severe obesity
  - which can be controlled externally by diet restrictions and behavior modification (2)
- Early diagnosis is important
  - to effective long-term management
  - prevent complications
  - prolong life expectancy
- Growth hormone treatment improves growth, physical phenotype and body composition (3)

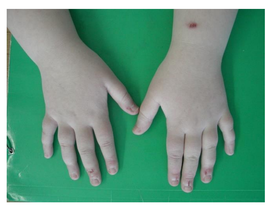
Case reports

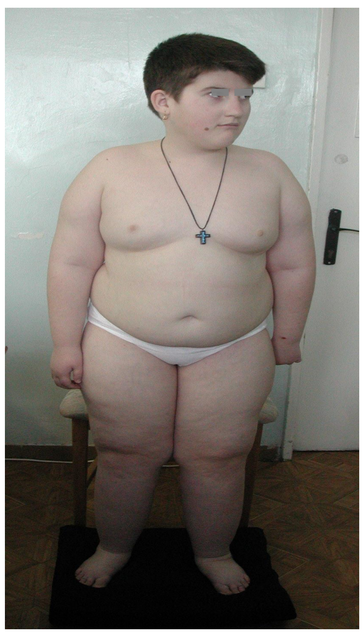
Case 1

Facies



Acromicria





Case 1.-Diana, 21 years

- only child of a non-consanguineous couple
- born at terme (34 w)
- weight 2200 g
- Apgar 7

❖first years of life:

- important hypotonia
- tube fed in the first 6 months
- mental and motor retardation
- hyperphagia started at 1st year of life
- general seizures by the age of 2
- sleep apnea

❖18 years old

- obesity - 84,3kg, BMI=34.6 kg/m2
- final height 156 cm (-0,5 SD)
- fat mass (electric impedance) 34%

❖Clinical examination

- narrow forehead
- discrete almond-shaped palpebral fissures
- acromicria
- genital development - telarche (B3-4)
- menarche absent
- important mental retardation

❖ Genetics

- at 8 years: caryotype 46, xx. test FISH: del (15) (q11.2-q13)

❖ Biological tests

•Normal thyroid and adrenal axes
•Normal estradiol and gonadotrophines
•IGF1 normal (138 ng/ml
• At 6 y, low GH (0,2 μg/l), insufficient clonidine stimulation (5,6 μ g/l)

Case 2.- Fabiana, 11 years

- only child of a non-consanguineous couple
- born at terme in 2005
- weight 2700g
- Apgar 8

❖first years of life:

- generalized hypotonia
- mental and motor retardation
- hyperphagia started after the 1st year of life

❖11 years old:

• obesity- 52 kg, BMI for children=27.3 kg/m2
• height: 137.5 cm, -1.2 DS
• puberty stage: BI-II PII
• bone age: 11 years

❖Clinical examination

- discrete almond-shaped palpebral fissures
- acromicria
- achantosis nigricans
- dental malposition
- Moderate mental retardation

❖ Genetics

- at 4 years: caryotype 46,xx; MS-PCR metilation 15q11.2-q13

❖ Biological tests

• mild hypothyroidism compensate with lT4
• normal adrenal function
•low IGF1=96.5 ng/ml (N: 111-551)
• low basal GH<0.05 ng/ml, without stimulation at the arginine test

Case 3.-Vlad, 27 years

- first child of a young non-consanguineous couple
- 1 healthy brother
- born at terme
- weight 3500g
- Apgar – no information

❖first years of life:

- generalized hypotonia
- psyghological and mental retardation
- hyperphagia started after the 1st year of life

❖17 years old

• obesity – 80kg
• final height 159 cm, -2.7 DS
• epiphyseal closure

❖Clinical examination

- discrete almond-shaped palpebral fissures
- Acromicria
- Genital hypoplasia
- severe sleep apnea
- moderate mental retardation

❖Genetics

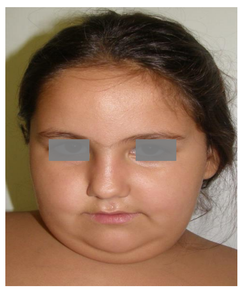
- caryotype 46,xx; del (15) (q11.2-q13)

❖ Biological tests

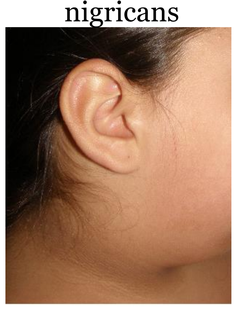
•Normal thyroid and adrenal axes
•Low IGF1 – 14,3 ng/ml (N:130-600)

Case 2

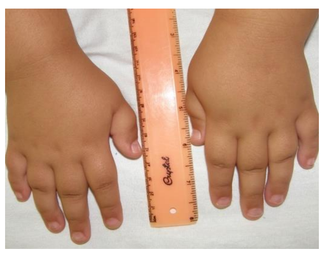
Facies

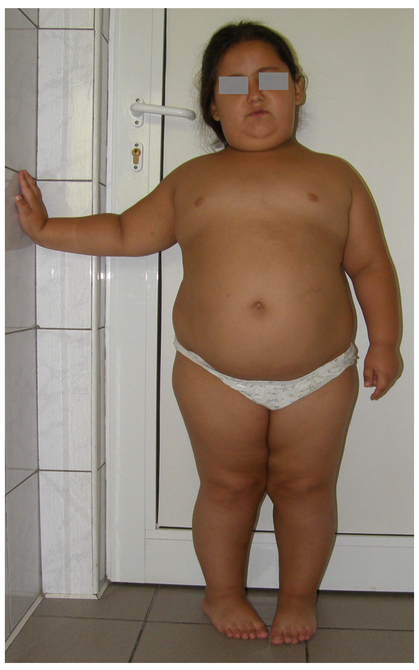


Achantosis nigricans



Acromicria





All pictures are reproduced with informed consent.

Discussions

❖Our 3 cases presented specific clinical features of PWS and genetic confirmation, but the therapeutic attitude was different for each case:

- **Case 1**:
  - at the age of 10, had important obesity (+10SD) and a surprising height at +2SD despite of partial GHD
  - her actual height remains higher than expected (-0.5SD)
  - although basal GH remains low and IGF1 at the inferior limit, the association of confirmed sleep apnea temporized the GH treatment
- **Case 2:**
  - at the age of 11, presented moderate obesity and a height of 137.5 cm (-1.2 DS)
  - the confirmed GHD, with the possible aggravation of obesity, in the absence of sleep apnea, justified the rhGH therapy
- **Case 3:**
  - had the first endocrinological examination at the age of 17 years and presented epiphyseal closure, with a final height of 159 cm (-2.7SD) and moderate overweight
  - in spite of confirmed GHD, no treatment was initiated because of parents' option

Conclusion

- With rigorous alimentation and constant psychological and parental support, the weight in our cases did not excessively increase.
- The benefits of GH treatment are substantial as it not only improves physical characteristics and psychomotor development, but also has psychological and behavioral benefits, the major concern being aggravation of sleep apnea.(4)
- Aggravation of pre-existing conditions due to GH therapy have been found in some individuals in literature and should be closely monitored.
- GH treatment is recommended and should be individualized for patients with PWS in conjunction with dietary, environmental and lifestyle interventions.(5)

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Syndromes : Mechanisms and Management

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