USO NO CONVENCIONAL DE GH EN EL SINDROME DE PRADER-WILLI

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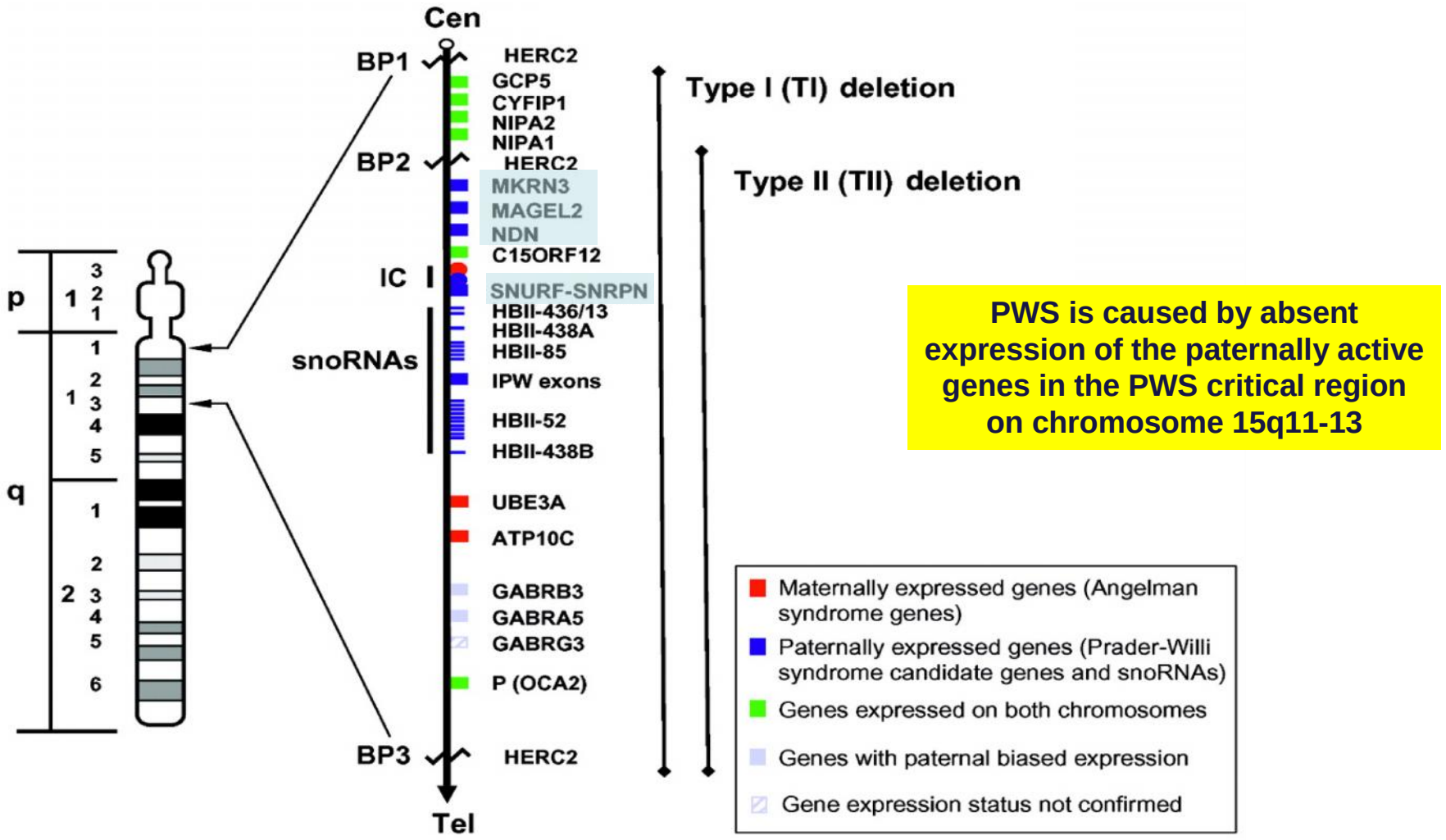
SINDROME DI PRADER-WILLI

- **forma più comune di obesità genetica**
- **prevalenza 1:20.000 ÷ 50.000**
- **causata da una alterazione del cromosoma 15**
  (*delezione, disomia uniparentale materna, difetto del centro dell'imprinting*)

- Patologia molto variabile che interessa molti organi e apparati.
- Il quadro clinico completo non è presente alla nascita.
- Alcuni segni clinici più caratteristici si renderanno più evidenti negli anni successivi.
- Ogni diversa epoca dello sviluppo si caratterizza per problematiche differenti.

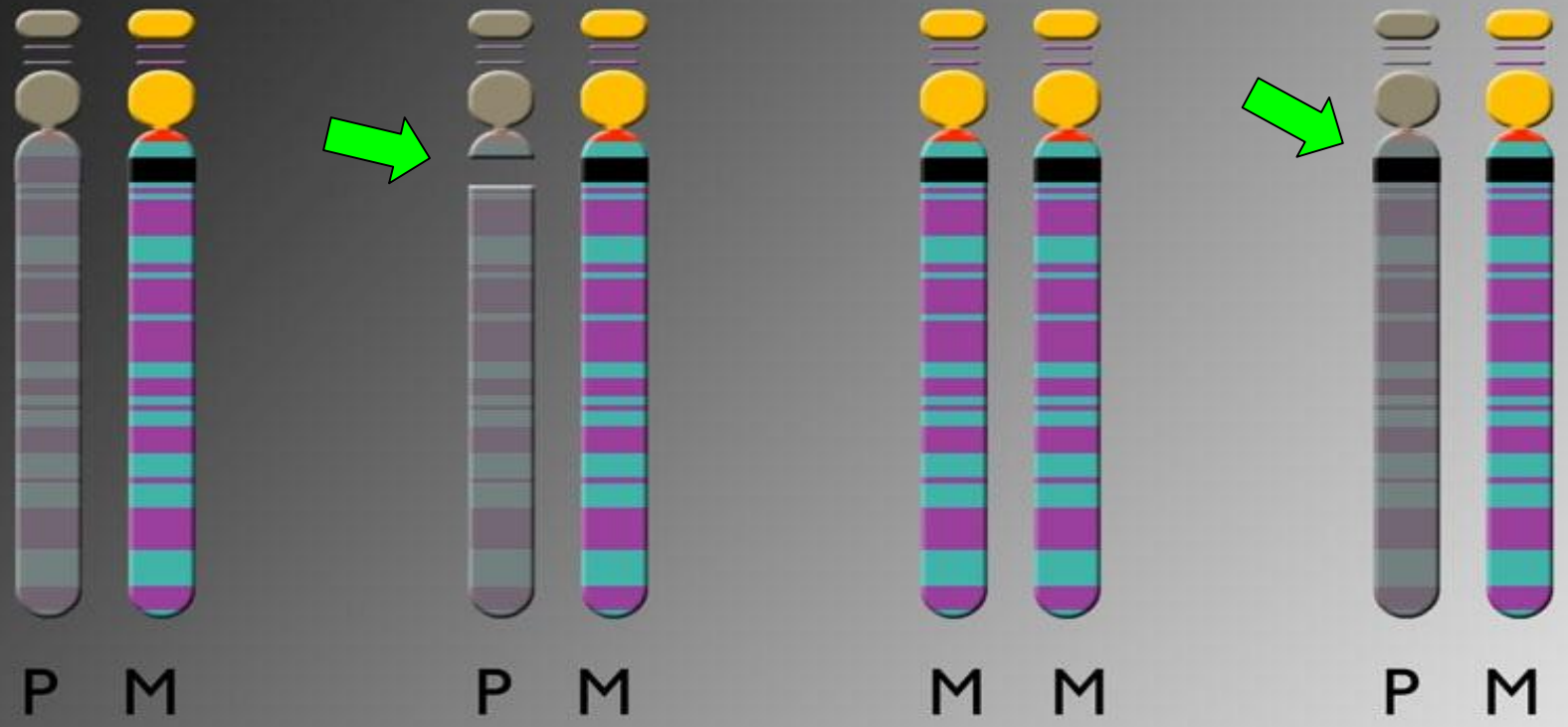
FIGURE 1 - High-resolution chromosome 15 ideogram, order of genes on 15q11-q13 region, and patterns of expression



Bittel, D. C. et al. Pediatrics 2006;118:e1276-e1283

PEDIATRICS®

Genetic Mechanisms Leading to Prader-Willi Syndrome



Normal chromosome 15

Deletion

75-80 %

Maternal UPD

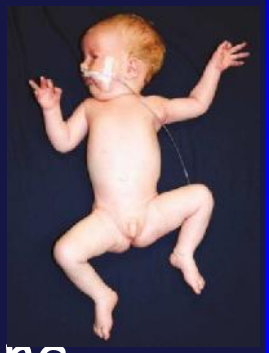
20-25 %

Imprinting Defect

1-2 %

Clinica della PWS in rapporto alle diverse fasce di età

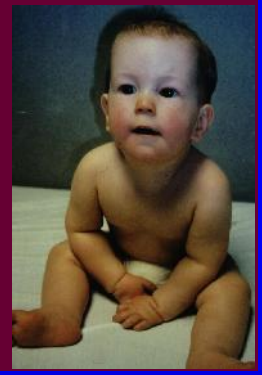
Stadio fetale e neonatale



- Ridotti movimenti fetali
- Ipotonia *(floppy baby)*
- Difficoltà nel succhiare
- Difficoltà di alimentazione
- Letargia e pianto flebile
- Ipoplasia dei genitali

Prima infanzia

- Ipotonia *(di origine centrale)*
- Scarsa crescita ponderale
- Tratti somatici caratteristici *(non frequenti a questa età)*
- Ritardo dello sviluppo psicomotorio
- Criptorchidismo



Acta Pædiatr 92: 1085–1089. 2003

Neonatal hypotonia: don't forget the Prader-Willi syndrome

G Trifirò[1], C Livieri[2], L Bosio[3], L Gargantini[4], A Corrias[5], G Pozzan[6] and A Crinò[7] and the Genetic Obesity Study Group of the Italian Society of Paediatric Endocrinology and Diabetology (SIEDP)

U.O. Neonatologia[1], Ospedale San Giuseppe, Milan; Dipartimento di Scienze Sanitarie Applicate e Psicocomportamentali[2], Pavia; Clinica Pediatrica[3], Centro di Endocrinologia Infantile e dell'Adolescenza, H San Raffaele, Milan; U.O. di Pediatria[4], Azienda Ospedaliera, Treviglio; Divisione di Endocrinologia Pediatrica[5], Ospedale Infantile Regina Margherita, Turin; Dipartimento di Pediatria[6], Padua; Unità di Malattie Endocrine Autoimmuni[7], IRCCS Ospedale Bambino Gesù, Rome, Italy

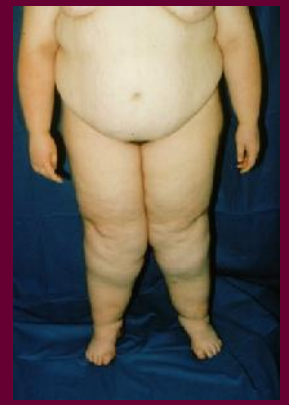
Clinica della PWS in rapporto alle diverse fasce di età

Bambino

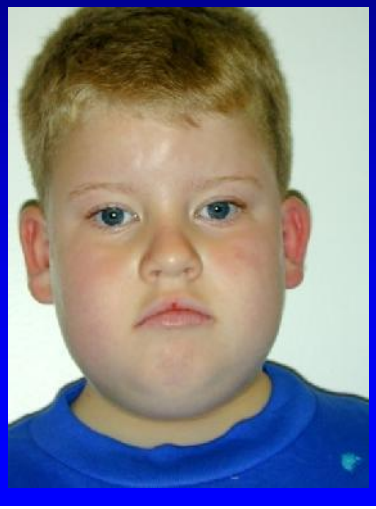
- Ipotonia *(migliorata)*
- Iperfagia
- Obesità
- Scoliosi e cifosi
- Strabismo, miopia
- Acromicria
- Difficoltà di alimentazione
- Carie dentaria
- Bassa statura
- Ritardo cognitivo/linguaggio

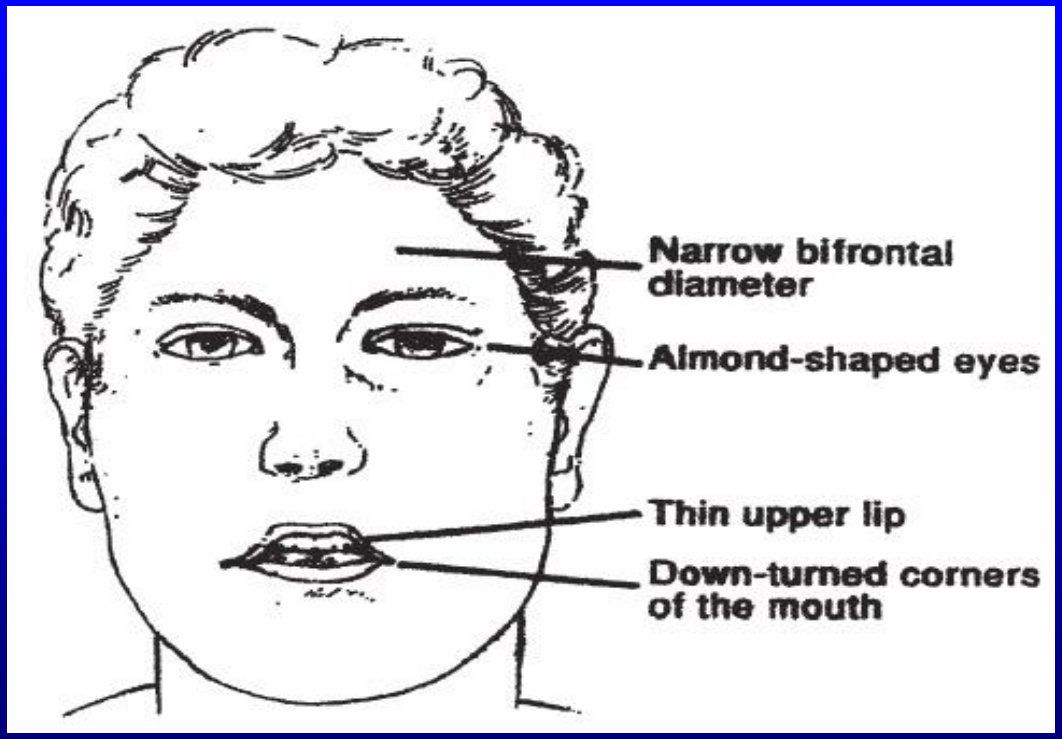
Adolescente

- Iperfagia e ricerca ossessiva di cibo
- Obesità severa
- Ipogonadismo/pubertà ritardata
- Disturbi comportamentali
- Scoliosi/cifosi
- Skin-picking
- Acromicria *(mani e/o piedi)*
- Narcolessia e apnee notturne
- Carie e paradontopatie *(saliva densa)*
- Alterazione metab. glicidico *(IGT, DM)*



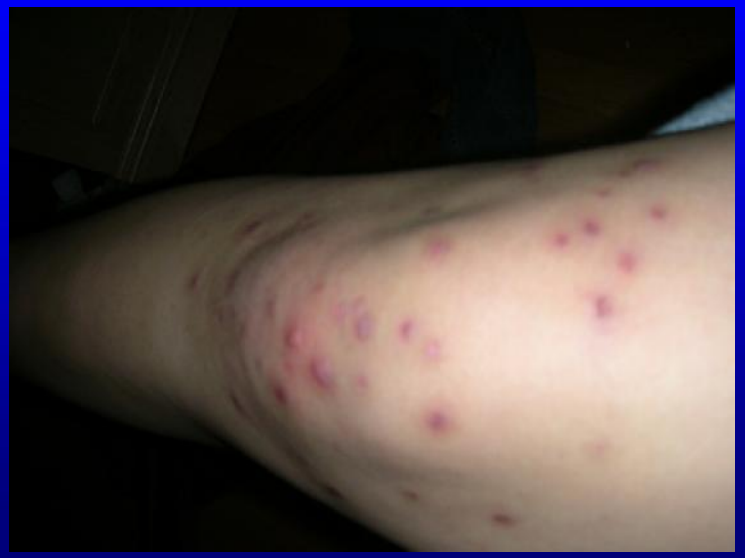
Caratteristiche del volto nella PWS

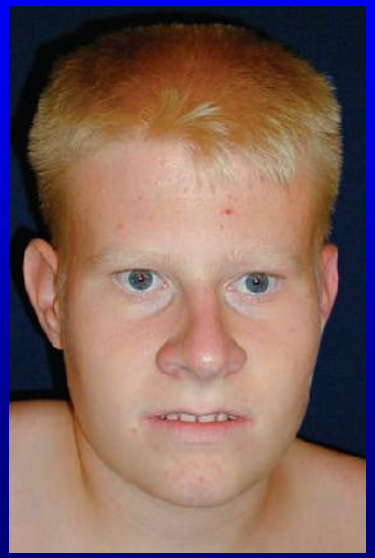




ALTRI SEGNI CLINICI NELLA PWS

- Ipopigmentazione cutanea – cute e capelli chiari
- Instabilità della temperatura nell'infanzia
- Alterazioni oculari *(strabismo ecc.)*
- Elevata soglia del dolore
- Diminuito senso del vomito
- Abilità nei puzzles
- Skin-picking e altri atti autolesionistici

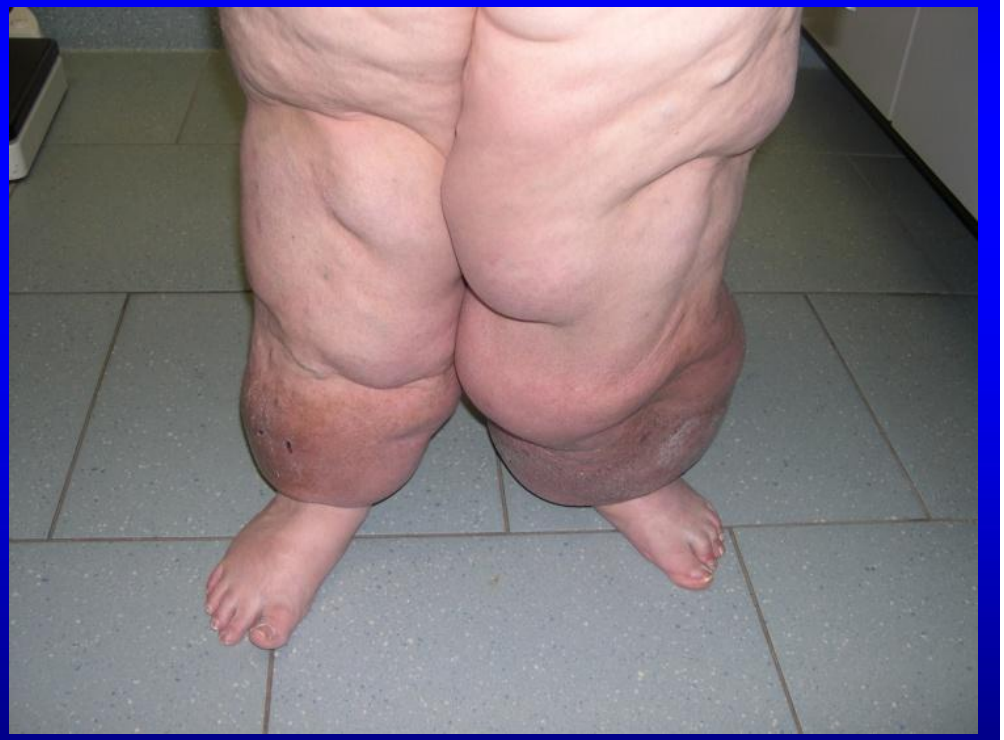




Clinica della PWS in rapporto alle diverse fasce di età

Ricerca ossessiva di cibo *(iperfagia)*
Obesità anche molto grave
Ipogonadismo *(multifattoriale)*
Acromicria
Ritardo cognitivo e linguaggio
Bassa statura *(per il target genetico)*
Osteoporosi
Carie e paradontopatie
Problemi comportamentali
Skin-picking
Saliva densa e vischiosa
Alterazione metabolismo glucidico
Ipertensione arteriosa
Sleep apnea syndrome *(centrali o ostruttive)*
Lipodistrofia arti inferiori

Età adulta



TURBE DEL CARATTERE e DEL COMPORTAMENTO nella PWS

COMPORTAMENTO LEGATO AL CIBO

Abbuffarsi, iperfagia, furto di cibo, ingerire materiale non edibile, mancanza di sazietà

COMPORTAMENTO AGGRESSIVO

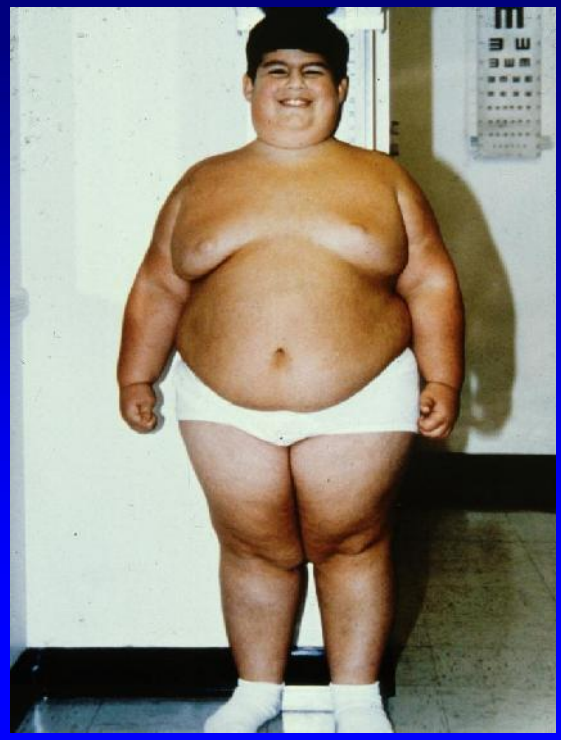
improvvisi e inspiegabili scatti d'ira, irragionevole, polemico, insistente, testardo, ossessivo, bugiardo, umore labile - *aumentata incidenza di psicosi*

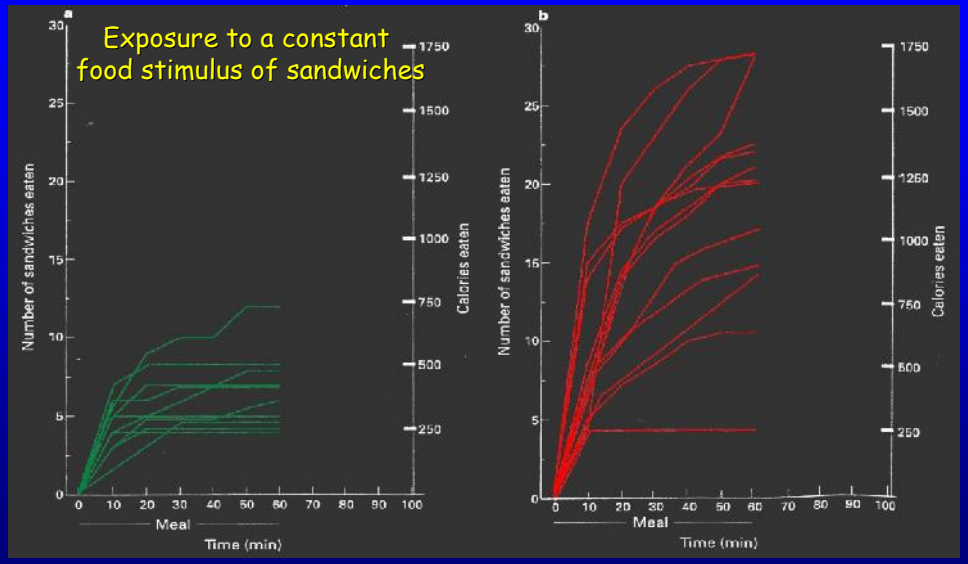
COMPORTAMENTO AUTOLESIONISTA

pizzicarsi la pelle *(skin-picking)*
altri atti autolesionistici

Obesità nella PWS

- Di tipo centrale – compare dopo i 2-4 aa
- Il grasso è per lo più localizzato all'addome, natiche, cosce *(risparmiate le mani e i piedi)*
- Massa grassa aumentata rispetto agli obesi semplici di pari peso - Ridotto grasso viscerale *(FFM)*
- Ridotta massa magra *(LBM)*
- Più frequente causa di morbilità e mortalità





adapted from Holland et al., Int J Obes 1993;17:527-32


obesity associated with PWS is often massive and many subjects exceed by more than 200% their IBW

Alterazione delle funzioni ipotalamiche nei pazienti con PWS

Principale organo danneggiato nella PWS

Funzioni alterate:

Secrezione endocrina

- *Ormone della crescita (GH)*
- *Gonadotropine*
- *Tiroide*
- *Surrene*

Controllo dell'appetito *(iperfagia)*

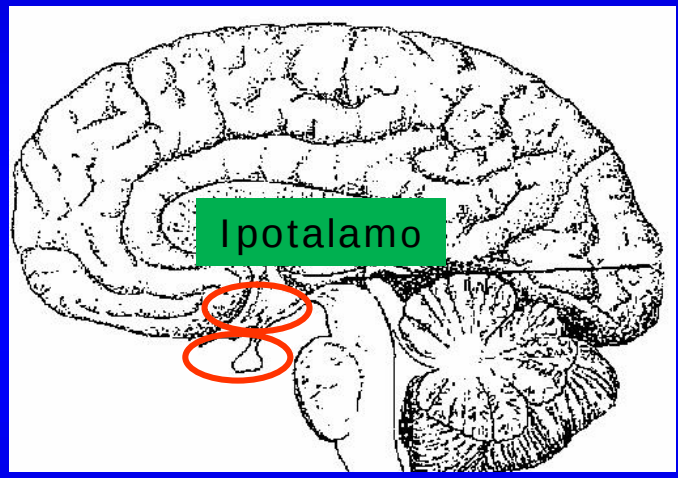
Disregolazione del Sistema Nervoso Autonomo

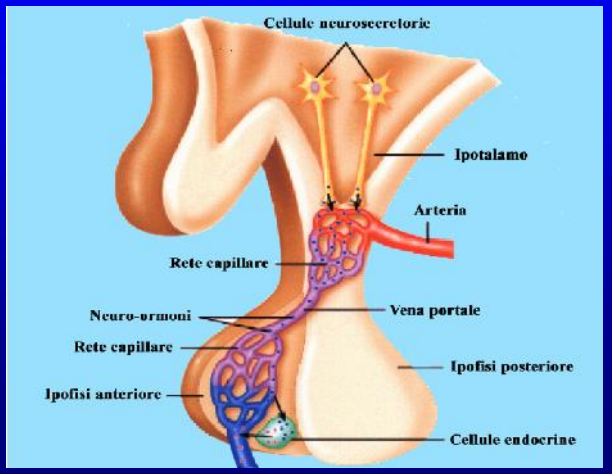
Bilancio idro-elettrolitico

Alterazioni del sonno notturno *(apnee centrali)*

Riduzione della memoria a breve termine

Instabilità della temperatura

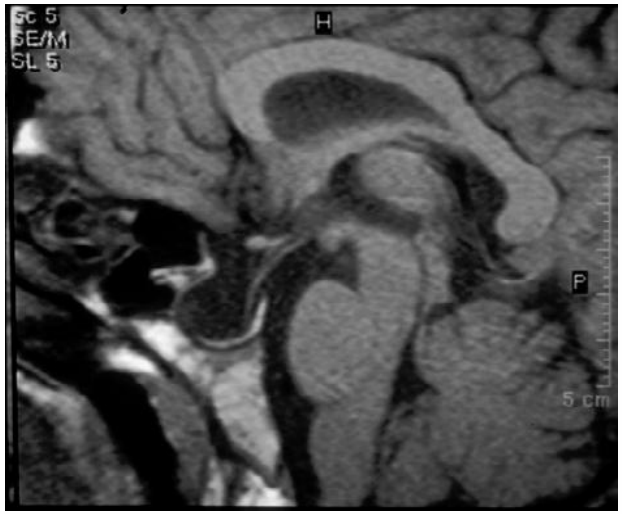




Eur J Pediatr
DOI 10.1007/s00431-007-0555-3

SHORT REPORT

Pituitary height and neuroradiological alterations in patients with Prader-Labhart-Willi syndrome

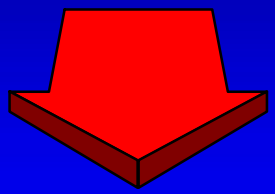


L. Iughetti · L. Bosio · A. Corrias · L. Gargantini · L. Ragusa · C. Livieri · B. Predieri · P. Bruzzi · G. Caselli · G. Grugni

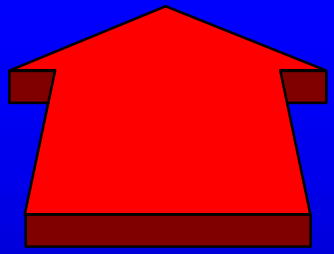
Received: 11 April 2007 / Accepted: 12 June 2007

Abstract Prader-Willi syndrome (PWS), a genetic disorder due to an alteration in the paternally derived long arm of chromosome 15, is characterized by a complex clinical picture (short stature, obesity, hypogonadism) that seems to be referable to as a central hypothalamic/pituitary dysfunction. To determine whether there is any diminution in the anterior pituitary gland or other neuroradiological alterations, we retrospectively analysed 91 patients with PWS (42 females, 49 males; age range: 0.7–16.8 years) by cerebral magnetic resonance imaging (MRI). Of these 91 patients, MRI analysis showed a reduction in pituitary height in 45 patients (49.4%), a complete absence of the posterior pituitary bright spot in six patients (6.6%) and other neuroradiological alterations in ten patients (11%). Altogether, neuroradiological alterations were present in 61 of the 91 (67%) patients. Our results indicate that

CRITERI CLINICO-ANAMNESTICI
(sec. HOLM e CASSIDY)



DIAGNOSI di SINDROME di PRADER-WILLI



INDAGINI GENETICHE
(alterazione del cromosoma 15)

TEST DI METILAZIONE *(MLPA)* è in grado di confermare la diagnosi nel 99 % dei casi sospetti

Indicazioni per l'invio alla diagnosi genetica *(sospetto PWS)*

Età	Caratteristiche cliniche
Nascita → 2 aa.	Ipotonia muscolare + suzione ipovalida, pianto flebile, criptorchidismo
2 → 6 anni	Ipotonia + Anamnesi positiva per suzione ipovalida, pianto flebile + Ritardo globale di sviluppo neuromotorio, criptorchidismo *(M)*, bassa statura con progressivo incremento ponderale
6 → 12 anni	Anamnesi di ipotonia *(che spesso persiste)* e suzione debole + Ritardo globale di sviluppo psicomotorio + Iperfagia e ossessività verso il cibo con obesità centrale *(se non controllata)*
13 anni → età adulta	Deficit cognitivo *(solitamente ritardo mentale di grado lieve-moderato)* + Iperfagia con obesità centrale *(se non controllata)* + Ipogonadismo e ritardo puberale + Disturbi comportamentali tipici *(accessi d'ira e manifestazioni compulsive di vario tipo)* + Anamnesi positiva per ipotonia, suzione ipovalida, pianto flebile

Gunay-Aygun et al, 2001 (modificata)

ACCRESCIMENTO in PWS non TRATTATI

- Neonato: *lunghezza normale (SGA 20-25%)*
- 1° anno: *normale crescita – bassa statura nel 50% dei casi*
- 3-13 anni: *progressivo rallentamento staturale - 50° centile PWS = 3° centile della popolazione generale*
- Pubertà: *ulteriore riduzione del pattern accrescitivo - assenza dello spurt puberale*

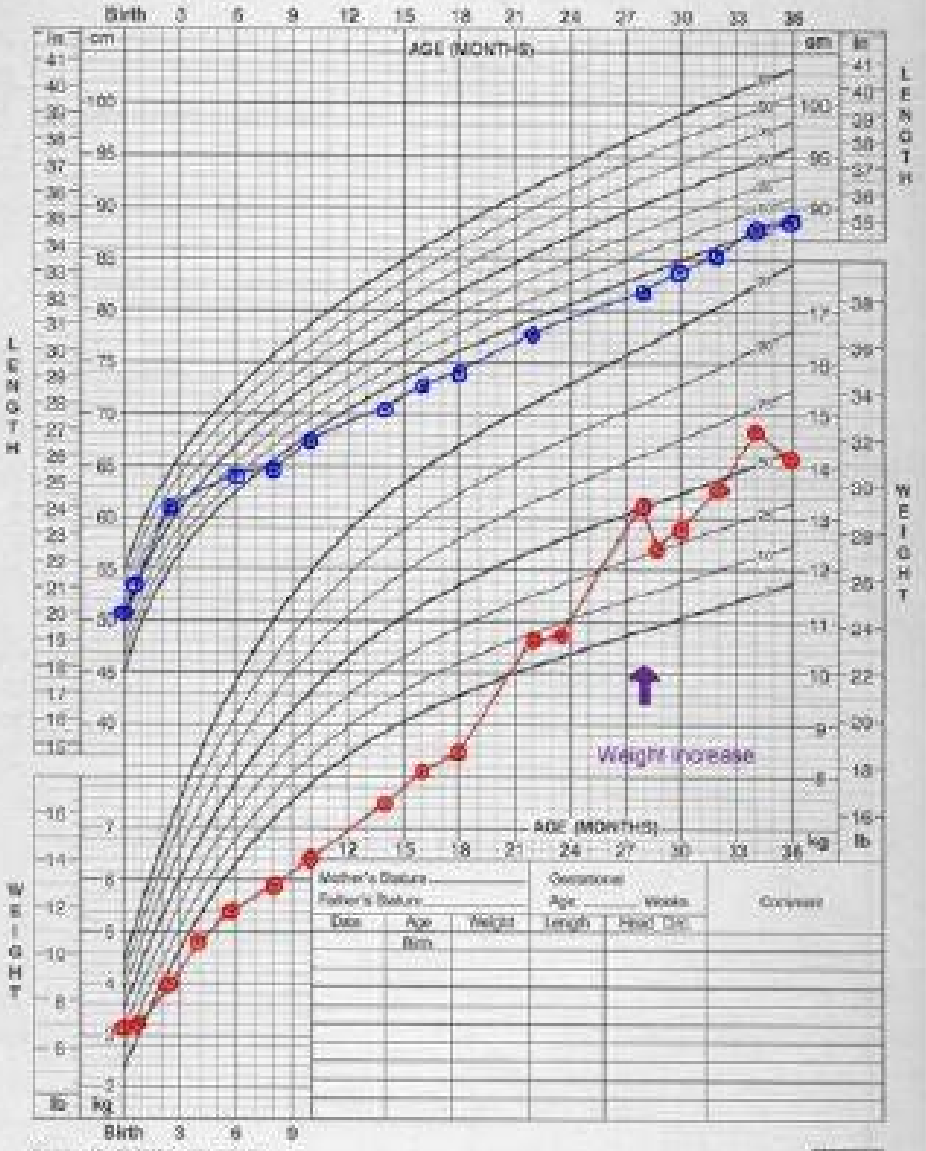
STATURA DEFINITIVA *(quasi sempre inferiore al target genetico):*
Maschi: 152 ÷ 162 cm - Femmine: 142 ÷ 150 cm

DP

Birth to 36 months: Boys
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 4/30/01)
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC

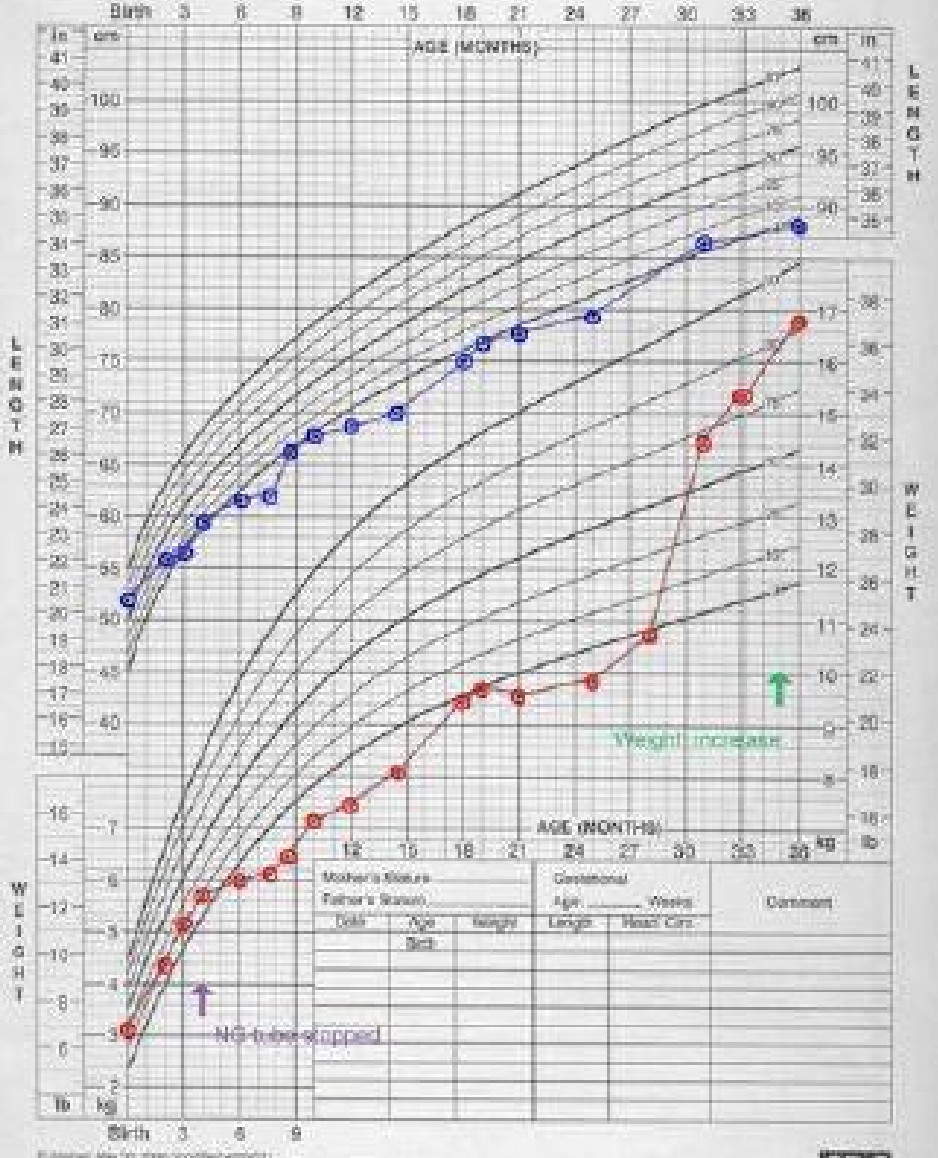
SAFER · HEALTHIER · PEOPLE

MP

Birth to 36 months: Boys
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



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SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC

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DIFETTO IPOTALAMICO di GH nella PWS

- Bassa statura *(diversamente dai soggetti con obesità semplice)*
- Diminuita velocità di crescita
- Ridotta massa magra
- Mani e piedi piccoli *(acromicria)*
- Bassi livelli di IGF-1 e di insulina
- Difetto di GH ai test di stimolo standard
- Effetti positivi della terapia con GH

Eiholzer et al, Horm Res 53 (suppl 3): 44-52, 2000

Caratteristiche della composizione corporea in pazienti con obesità semplice e con PWS

Studi effettuati con DEXA, TAC o RMN	Obesità semplice	PWS
• Massa Magra	aumentata	diminuita
massa muscolare	*aumentata*	*diminuita*
massa ossea	*aumentata*	*diminuita*
• Massa Grassa	aumentata	aumentata
grasso viscerale	*aumentata*	*diminuito*
grasso del tronco	*aumentato*	*aumentato*
• Massa Magra/ Massa Grassa	diminuito	diminuito

J. Endocrinol. Invest. *23:* 84-89, 2000

GH/IGF-I axis in Prader-Willi syndrome: Evaluation of IGF-I levels and of the somatotroph responsiveness to various provocative stimuli

A. Corrias*, J. Bellone*, L. Beccaria**, L. Bosio**, G. Trifirò***, C. Livieri****, L. Ragusa*****, A. Salvatoni******, M. Andreo*, P. Ciampalini********, G. Tonini*******, A. Crinò********, and Genetic Obesity Study Group of Italian Society of Pediatric Endocrinology and Diabetology

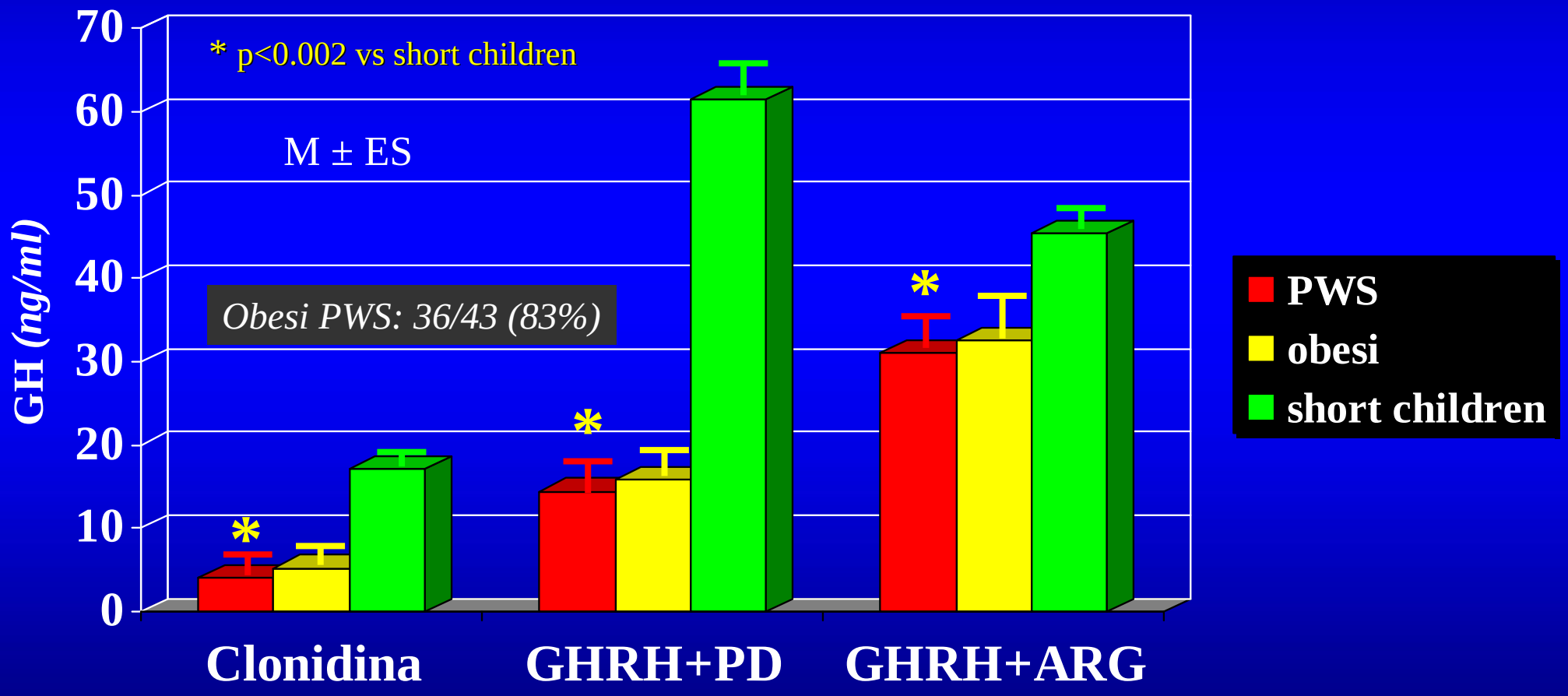
*Division of Pediatric Endocrinology, Regina Margherita Hospital, Turin; **Department of Pediatrics, Endocrine Unit, Scientific Institute, San Raffaele Hospital, University of Milan; ***Department of Pediatrics, Sacco Hospital, Milan; ****Department of Pediatrics, University of Pavia; *****Department of Pediatrics, OASI Institute, Troina, Enna; ******Department of Pediatrics, Circolo Hospital, Varese; *******Department of Pediatrics, Burlo Garofalo Hospital, Trieste; ********Division of Endocrinology, Bambino Gesù Hospital, Rome, Italy

ABSTRACT. Basal IGF-I levels and the GH response to at least two among provocative stimuli such as clonidine (CLO, Catapresan, 150 mcg/m^2 po), GHRH (1 mcg/kg iv)+arginine (ARG, 0.5 g/kg iv infusion during 30 min) and GHRH+pyridostigmine (PD, Mestinon cpr 60 mg po) have been evaluated in 43 children with Prader-Willi syndrome (PWS, 17 males and 26 females, age 3-22 yr, 7 normal weight and 36 obese PWS), in 25 normal short children (NC, 17 males and 8 females, 7.7-18.5 yr) and in 24 children with simple obesity (OB, 14 males, 10 females, 7.7-21.5 yr). Both normal weight and obese PWS had mean IGF-I levels lower than those recorded in NC ($p<0.001$) and OB ($p<0.001$). The GH responses to GHRH+ARG and GHRH+PD in NC were similar and higher than that to CLO ($p<0.001$). In PWS the GH response to GHRH+ARG was higher than that to GHRH+PD ($p<0.001$) which, in turn, was higher than that to CLO ($p<0.001$); these responses in PWS were lower than those in normal children ($p<0.02$) and similar to those in OB. In normal weight PWS the GH responses to GHRH+ARG and to GHRH+PD were similar and higher than to CLO ($p<0.05$); however, each provocative stimulus elicited a GH rise lower than that in NC ($p<0.05$). In obese PWS as well as in OB the GH response to GHRH+ARG was higher than that to GHRH+PD ($p<0.02$) which, in turn, was higher than that to CLO ($p<0.001$); all GH responses in obese PWS and OB were lower than those in NC ($p<0.001$) but similar to those in normal weight PWS. In conclusion, patients with PWS show clear reduction of IGF-I levels as well as of the somatotroph responsiveness to provocative stimuli independently of body weight excess. These results strengthen the hypothesis that PWS syndrome is frequently connoted by GH insufficiency.

(J. Endocrinol. Invest. *23:* 84-89, 2000)

Risposta del GH ai tests di stimolo

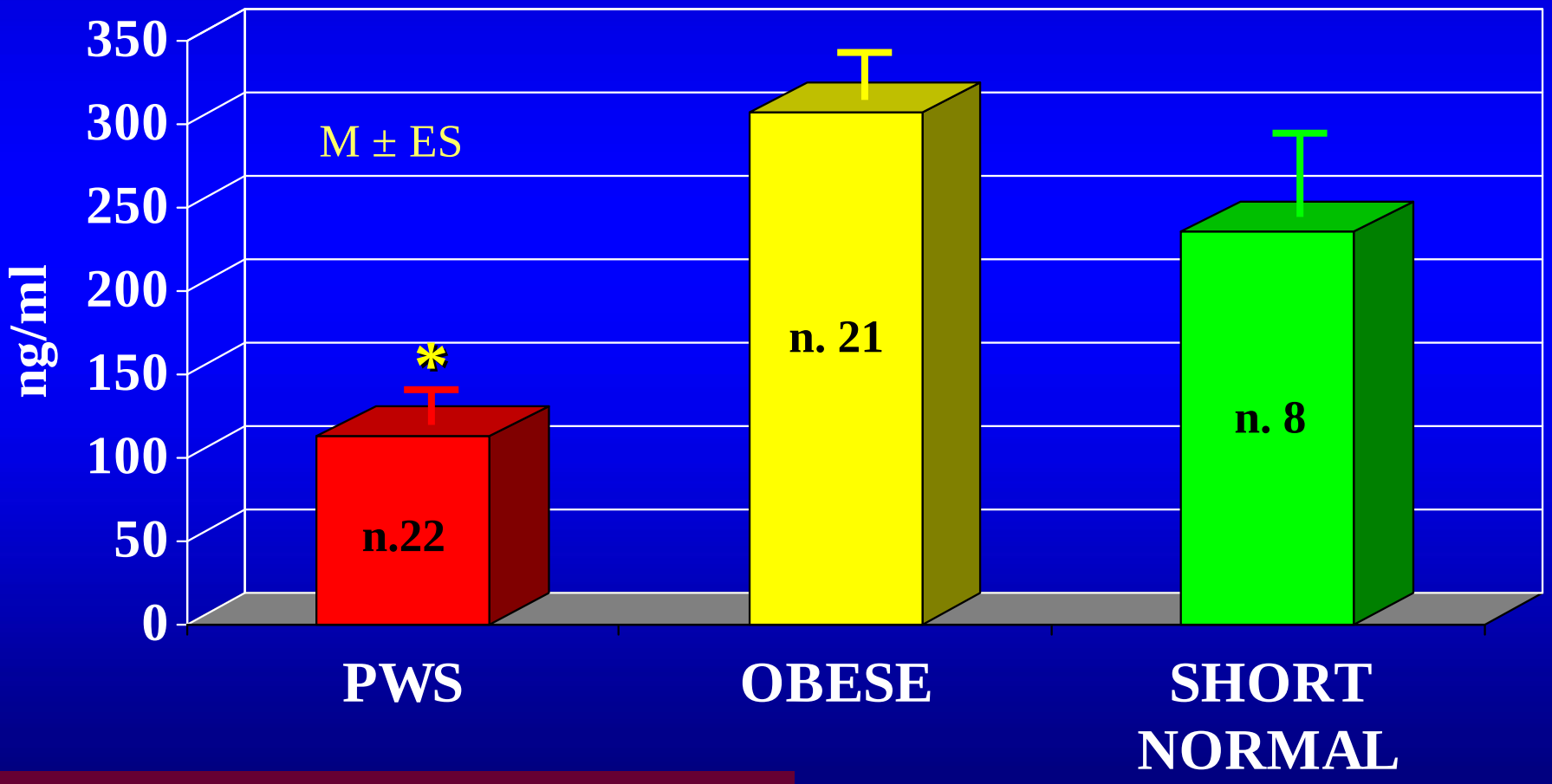
n. 43 PWS (17 m, 26 f - età 3-22 anni)



A. Corrias et al, J. Endocrinol Invest 23: 84-89, 2000

IGF-1 LEVELS in PWS

* *p < 0.0005 vs.obese e p < 0.001 vs short normal*



Grugni G. et al, Clin Endocrinol 48:769-775,1998

Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr
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n. 27 < 5yrs

Growth Hormone Response to Standard Provocative Stimuli and Combined Tests in Very Young Children with Prader-Willi Syndrome

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Sabrina Spera[a] Marina Cuttini[b] Marco Cappa[c] Antonino Crinò[a]

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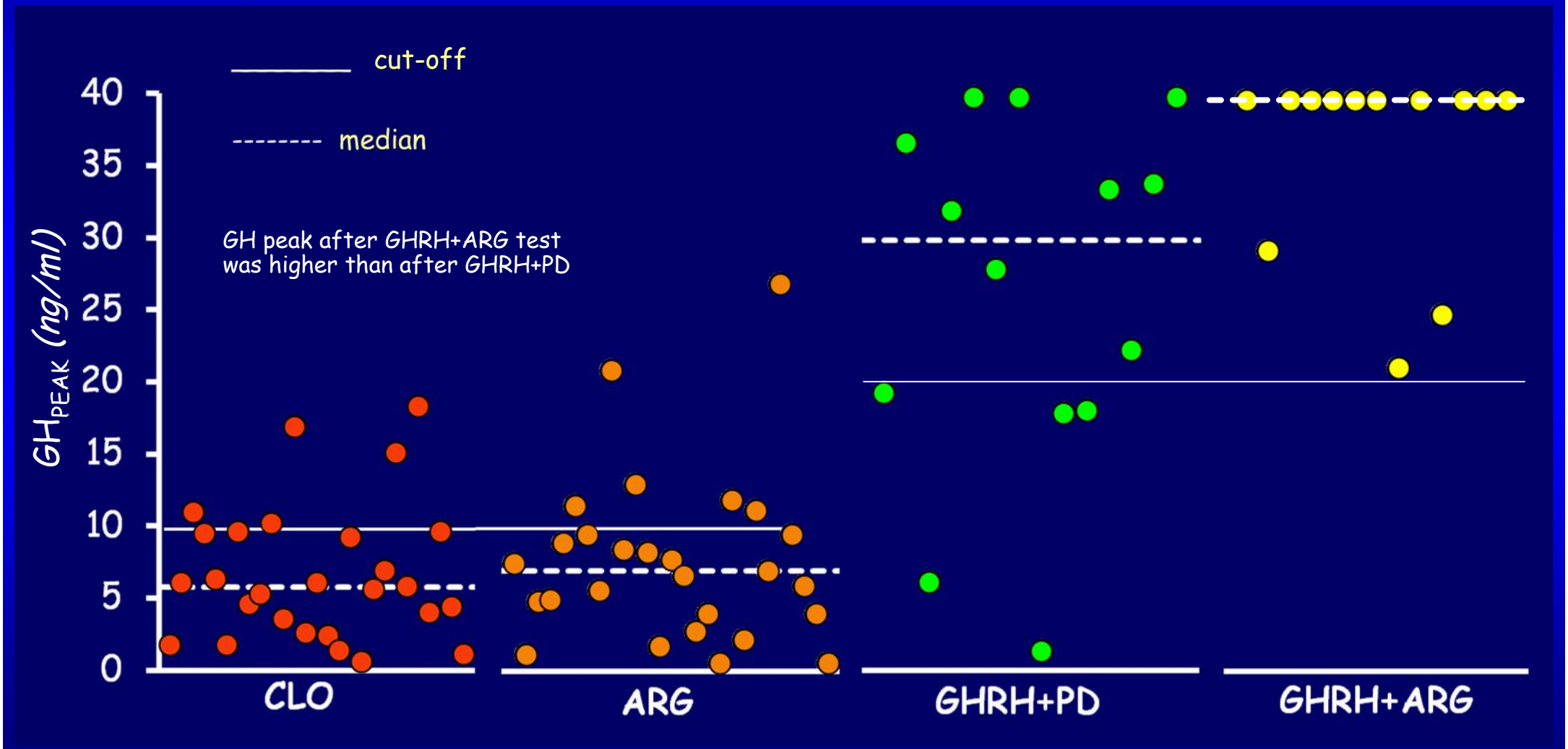
growth factor-1 (IGF-1) levels were also measured. ***Results:*** While standard tests (CLO and ARG) showed low GH peak in 85.2 and 70.4% of the patients, respectively, the combined test was found to be normal in 85.2%. IGF-1 was low in 66.7% of patients. Out of 27 patients, 3 (11%) showed a normal GH peak with both standard tests (group A), 6 (22%) to one of the standard tests (group B) and 18 (67%) presented a low response to both standard tests (group C). Four subjects showed low response to both the combined and standard tests and reduced IGF-1. ***Conclusion:*** Our data suggest that very young PWS children seem to have impaired hypothalamic GHRH secretion with a normal GH pituitary reserve.

Growth hormone secretion in PWS

27 patients *(12 female, 15 male)* - age: 2.3 ± 1.3 yrs *(range: 0.5 ÷ 5 yrs; median: 1.9 yrs)*



A. Crinò et al, 2014 Horm Res

BENEFICI DELLA TERAPIA CON GH NELLA PWS

Two adolescent girls with Prader-Willi syndrome: One *(left)* received GH treatment for 4 years; the other *(right)* received no GH treatment

- Migliora la velocità di crescita e prob. la statura finale
- Riduce il grasso corporeo e il body mass index *(BMI)*
- Aumenta la massa magra *(lean body mass)*
- Migliora la densità minerale corporea *(BMD)*
- Normalizza le proporzioni delle mani e dei piedi
- Aumenta lo sviluppo muscolare e la performance fisica
- Migliora l'ipotonia
- Migliora la funzione dei muscoli respiratori
- Aumenta la spesa energetica a riposo *(REE)*
- Migliora alcuni fattori di rischio cardiovascolare
- Modifica l'aspetto fenotipico *(se iniziata precocemente)*

Normalization of the body and facial phenotype of PWS following treatment with GH from infancy

From S.B. Cassidy, D.J. Driscoll, E J Hum Genet, 2008
From E Scheermeyer,, Aust Fam Physician. 2013

Neuroscience and Biobehavioral Reviews 36 (2012) 1817–1838

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Review

The effect of growth hormone treatment or physical training on motor performance in Prader–Willi syndrome: A systematic review

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ABSTRACT

Although motor problems in Prader–Willi syndrome (PWS) are prominent in infants, and continue into childhood and adulthood, there is little insight into the factors important for clinical management. The literature was reviewed to: (1) provide an overview of the characteristics and prevalence of motor problems and (2) evaluate the effects of growth hormone (GH) treatment and physical training on motor performance. A systematic search revealed 34 papers: 13 on motor performance; 12 on GH treatment; and nine on physical training. In infants, motor development is 30–57% of the normal reference values, and children and adults also have significant problems in skill acquisition, muscle force, cardiovascular fitness, and activity level. GH treatment positively influenced motor performance in infants, children, and adults, although not all studies demonstrated an effect. All studies on physical training demonstrated beneficial effects in PWS patients. We suggest a combination of GH treatment and physical training to be started as soon as possible, especially in infants, to improve motor development as this will positively influence general development.

Clinical Endocrinology (2008) 68, 919–925 doi: 10.1111/j.1365-2265.2007.03126.x

ORIGINAL ARTICLE

Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader–Willi syndrome

D. A. M. Festen*, M. Wevers*, A. C. Lindgren†, B. Böhm†, B. J. Otten‡, J. M. Wit§, H. J. Duivenvoorden¶ and A. C. S. Hokken-Koelega*,**

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Conclusion One year of GH treatment significantly improved mental and motor development in PWS infants compared to randomized controls.

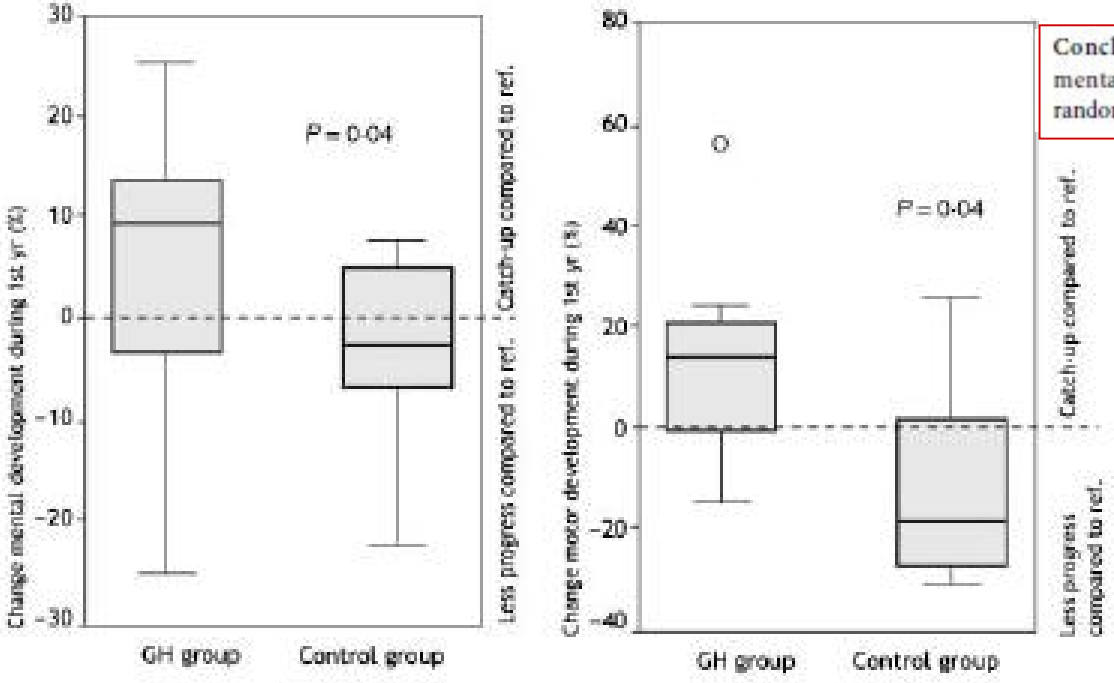


Fig. 2 Changes in mental and motor development during 12 months of study. The lower boundary of the boxplot is the 25th percentile and the higher boundary is the 75th percentile. The line in the box represents the median. Lines are drawn from the smallest to the largest observed value that is not an outlier. The horizontal line represents no change compared to normal children (change of 0%). A positive value represents a catch-up, compared to normal children, whereas a negative value represents less progress compared to normal children.

Beneficial Effects of Growth Hormone Treatment on Cognition in Children with Prader-Willi Syndrome: A Randomized Controlled Trial and Longitudinal Study

Elbrich P. C. Siemensma, Roderick F. A. Tummers-de Lind van Wijngaarden, Dederieke A. M. Festen, Zyrhea C. E. Troeman, A. A. E. M. (Janielle) van Alfen-van der Velden, Barto J. Otten, Joost Rotteveel, Roelof J. H. Odink, G. C. B. (Karen) Bindels-de Heus, Mariette van Leeuwen, Danny A. J. P. Haring, Wilma Oostdijk, Gianni Bocca, E. C. A. Mieke Houdijk, A. S. Paul van Trotsenburg, J. J. Gera Hoorweg-Nijman, Hester van Wieringen, René C. F. M. Vreuls, Petr E. Jira, Eelco J. Schroor, Evelyn van Pinxteren-Nagler, Jan Willem Pilon, L. (Bert) Lunshof, and Anita C. S. Hokken-Koelega

Methods: Fifty prepubertal children aged 3.5 to 14 yr were studied in a randomized controlled GH trial during 2 yr, followed by a longitudinal study during 4 yr of GH treatment. Cognitive functioning was measured biennially by short forms of the WPPSI-R or WISC-R, depending on age. Total IQ (TIQ) score was estimated based on two subtest scores.

Conclusions: Our study shows that GH treatment prevents deterioration of certain cognitive skills in children with PWS on the short term and significantly improves abstract reasoning and visuospatial skills during 4 yr of GH treatment. Furthermore, children with a greater deficit had more benefit from GH treatment. (*J Clin Endocrinol Metab* 97: 0000–0000, 2012)

La terapia con GH nel PWS adulto

- In questi ultimi anni è comparso un numero significativo di lavori relativi all'impiego di GH nei PWS adulti.
- Si è dimostrata un'azione positiva sia sulla composizione corporea, che sull'apparato cardiovascolare, la forza muscolare e gli aspetti psicologici.
- Non si ha viceversa alcuna azione sul peso corporeo.

Clinical Endocrinology (2006) 65, 492–499 doi: 10.1111/j.1365-2265.2006.02621.x

ORIGINAL ARTICLE

Impairment of GH responsiveness to combined GH-releasing hormone and arginine administration in adult patients with Prader-Willi syndrome

G. Grugni*, P. Marzullo†, L. Ragusa‡, A. Sartorio*, G. Trifirò§, A. Liuzzi† and A. Crinò¶ (on behalf of the Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology)

*Department of Auxology and †Department of Internal Medicine, S. Giuseppe Hospital, Research Institute, Italian Auxological Institute Foundation, Verbania, ‡Department of Pediatric Endocrinology, Oasi Maria S.S., Research Institute, Troina (EN), §Department of Pediatric Endocrinology, S. Giuseppe Hospital, Milan, ¶Unit of Autoimmune Endocrine Diseases, Bambino Gesù Children's Hospital, Research Institute, Palidoro-Rome, Italy

Summary

Objective It is unclear if poor health outcomes of adult patients with Prader-Willi syndrome (PWS) are influenced by GH deficiency (GHD). Few studies have been focused on PWS adults, but further information on the concomitant role of obesity on GH/IGF-I axis function is needed. The aim of our study was to investigate the prevalence of GHD in a large group of adult subjects with genetically impaired GH response was combined with subnormal IGF-I levels in all PWS patients with GHD.

Conclusions Adult subjects with PWS had a reduced responsiveness to GHRH + ARG administration associated with reduced IGF-I levels. In addition, a severe GHD for age was demonstrated in a significant percentage of PWS subjects. These findings are in agreement with the hypothesis that a complex derangement of hypothalamus-pituitary axis occurred in PWS, and suggested that impaired GH secretion is not an artefact of obesity.

The reduced responsiveness to both these combined tests in adult PWS patients does not seem to be an artefact of obesity.

Clinical Endocrinology (2012) 77, 86–93 doi: 10.1111/j.1365-2265.2011.04303.x

ORIGINAL ARTICLE

Effects of recombinant human growth hormone therapy in adults with Prader–Willi syndrome: a meta-analysis

134 PWS Adults

Ruth Sanchez-Ortiga*,†, Anne Klibanski*,‡ and Nicholas A. Tritos*,‡

*Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA, †Department of Endocrinology, Hospital General Universitario Alicante, Alicante, Spain and ‡Harvard Medical School, Boston, MA, USA

Summary

Objective Prader–Willi syndrome (PWS) is associated with GH deficiency, deleterious changes in body composition and function. As the effects of recombinant human GH (rhGH) in PWS adults have not been well established, we sought to conduct a meta-analysis of pertinent studies.

Design Meta-analysis of studies examining the effects of rhGH therapy in PWS adults.

Patients One hundred and thirty four PWS adults (75 men, 59 women).

Measurements Literature searches, including publications (PubMed, EMBASE and the Cochrane Register), and abstracts presented at meetings through July 2011 describing studies of rhGH therapy in PWS adults; 8/1194 articles, describing unique cohorts, were included. Two authors independently extracted data and examined study quality.

Results rhGH therapy for 12 months led to [weighted mean difference (95% CI)] decreased body fat [−2·91% (−3·90, −1·91)], visceral [−32·97 cm^2 (−55·67, −10·26)] and subcutaneous adiposity [−55·24 cm^2 (−89·05, −21·44)], and increased lean body mass (LBM) [2·41 Kg (1·32, 3·49)]. Similar changes in body fat [−2·89% (−4·69, −1·07)] and LBM [2·82 Kg (1·31, 4·33)] were found in longer studies. There were no changes in body mass index (BMI) or lipids. There was a small increase in fasting glucose [0·27 mmol/l (0·05, 0·49)] and trends towards higher fasting insulin [20·24 pmol/l (−0·55, 41·02)] and insulin resistance [HOMA: 0·60 (−0·04, 1·24)] after rhGH therapy for 12 months.

Conclusions In PWS adults, rhGH therapy led to decreased body adiposity and increased LBM without changes in BMI or lipids. There was a small increase in fasting glucose and trends towards higher insulin and insulin resistance.

J Clin Endocrin Metab. First published ahead of print March 29, 2013 as doi:10.1210/jc.2012-3888

Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome

Cheri L Deal,[1] Michèle Tony[2], Charlotte Höybye[3], David B. Allen[4], Maïthé Tauber[5], Jens Sandahl Christiansen[6], and the 2011 GH in PWS Clinical Care Guidelines Workshop Participants.[a]

Conclusions: Following a multi-disciplinary evaluation preferably by experts, rhGH treatment should be considered for patients with genetically-confirmed PWS in conjunction with dietary, environmental and lifestyle interventions. Cognitive impairment should not be a barrier to treatment, and informed consent/assent should include benefit/risk information. Exclusion criteria should include severe obesity, uncontrolled diabetes mellitus, untreated severe obstructive sleep apnea, active cancer or psychosis. Clinical outcome priorities should vary depending upon age and the presence of physical, mental and social disability, and treatment should be continued for as long as demonstrated benefits outweigh the risks.

J Clin Endocrin Metab. First published ahead of print September 3, 2013 as doi:10.1210/jc.2013-2012

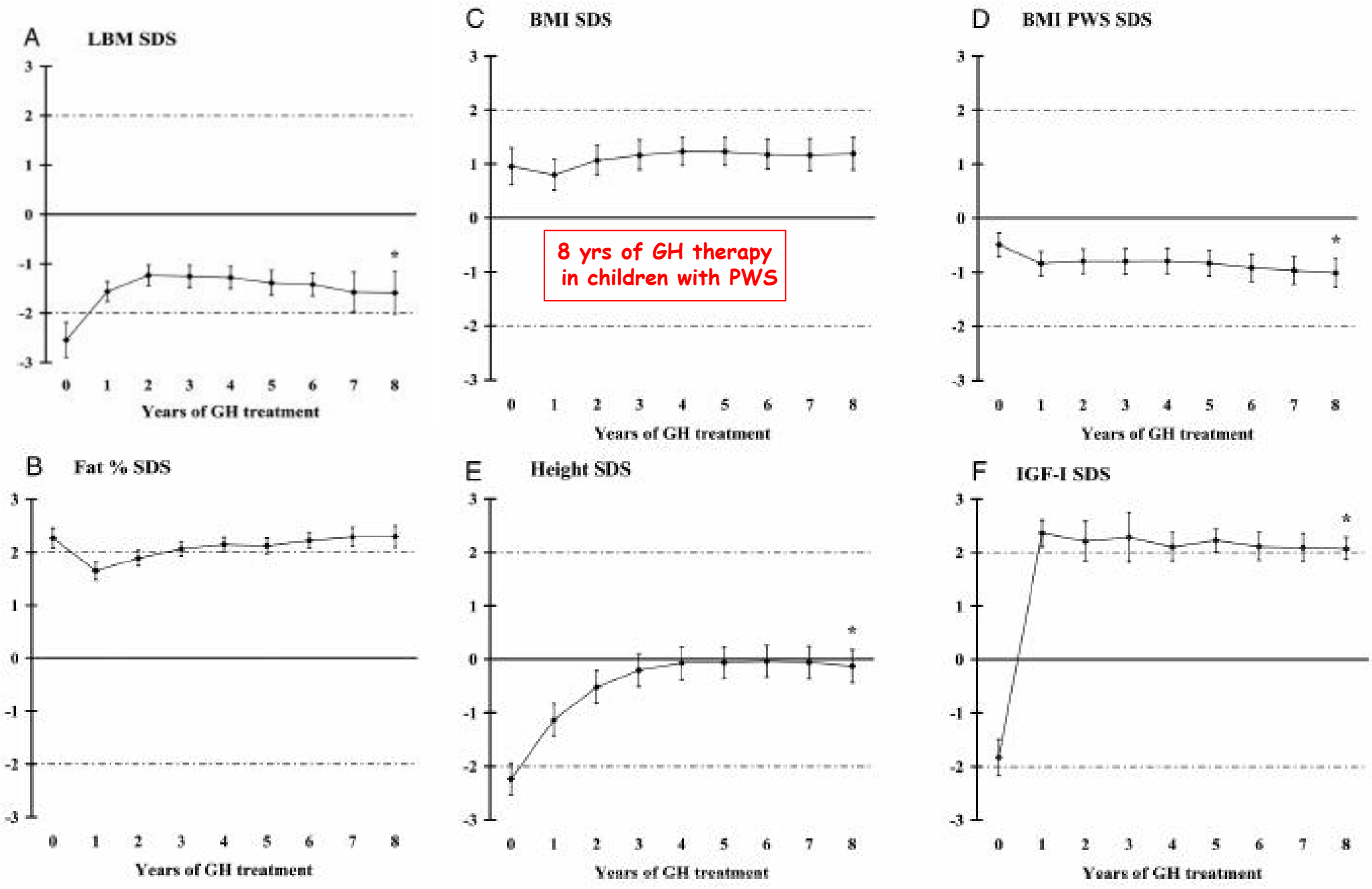
ORIGINAL ARTICLE

Endocrine Care

Eight Years of Growth Hormone Treatment in Children With Prader-Willi Syndrome: Maintaining the Positive Effects

60 prepubertal children
(GH: 1 mg/m2/d)

N. E. Bakker, R. J. Kuppens, E. P. C. Siemensma, R. F. A. Tummers-de Lind van Wijngaarden, D. A. M. Festen, G. C. B. Bindels-de Heus, G. Bocca, D. A. J. P. Haring, J. J. G. Hoorweg-Nijman, E. C. A. M. Houdijk, P. E. Jira, L. Lunshof, R. J. Odink, W. Oostdijk, J. Rotteveel, E. J. Schroor, A. A. E. M. Van Alfen, M. Van Leeuwen, E. Van Pinxteren-Nagler, H. Van Wieringen, R. C. F. M. Vreuls, N. Zwaveling-Soonawala, M. A. J. de Ridder, and A. C. S. Hokken-Koelega*



NE Bakker et al, JCEM 98: 2013

Terapia con GH nella sindrome di Prader-Willi

Quando cominciare

- intorno al primo anno di vita *(al più presto possibile)*

Quale dosaggio

- **Bambini**: 0.2÷0.25 mg/kg/sett; 0.025÷0.035 mg/kg/die; 1 mg/m^2/die
- **Adulti**: 0.03-0.08 mg/kg/settimana; 0.2 mg/die
- Somministrazione: 6-7 gg la settimana
- IGF-1 ⟶ *indicatore di adeguatezza terapeutica (<2 DS)*

Quando interrompere

- aumento incontrollato di peso
- alterazioni metaboliche *(ridotta tolleranza al glucosio, diabete)*
- disturbi respiratori *(e/o alterazioni polisonnografiche)*
- complicanze ortopediche rapidamente evolutive

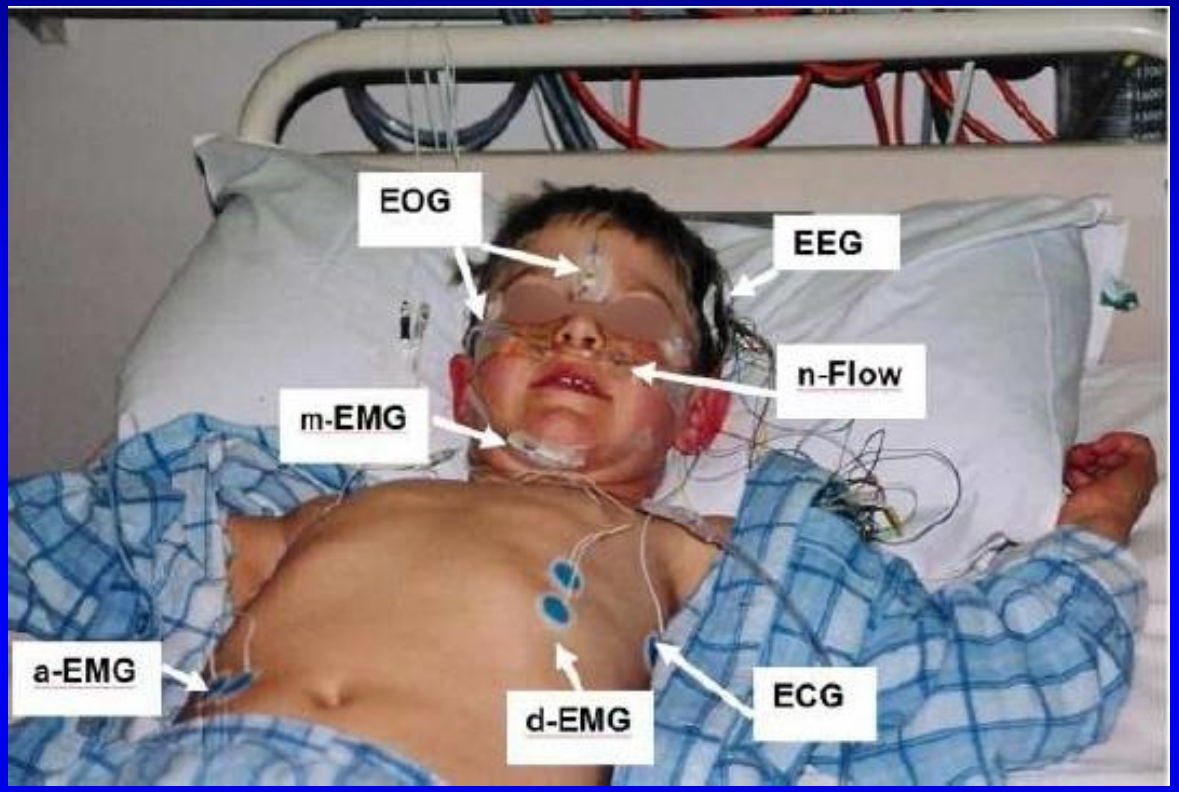
Raccomandazioni sull'uso dell'ormone della crescita nel bambino PWS

Prima di iniziare la terapia

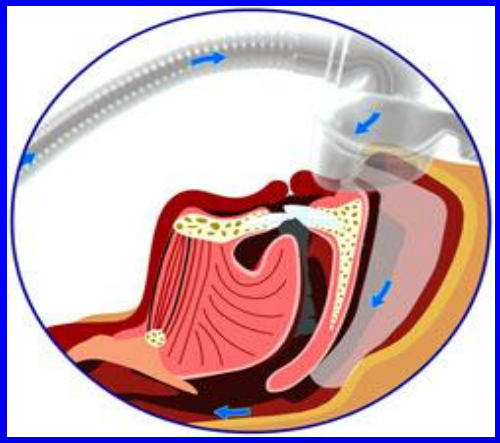
- Accurata valutazione clinica, nutrizionale e auxologica
- Funzione tiroidea *(FT4,TSH)*
- Glicemia, insulinemia, HbA1c
- OGTT *(se >2-3anni o se obesità e famil. DM)*
- IGF-1, IGF-BP3, *event. tests di stimolo per GH*
- Polisonnografia
- Valutazione otorinolaringoiatrica *(event. tonsillectomia)*
- Rx colonna vertebrale *(a qualsiasi età)* - età ossea
- Composizione corporea (DEXA) *(se possibile)*
- Valutazione cardiologica, cognitiva e neuropsichiatrica
- Valutazione surrenalica *(ACTH test?)*

A. Goldstone et al, JCEM, 93 (11): 4183-4197, 2008
CL Deal et al, JCEM 98 (6): E1072-1087, 2013

Polisonnografia



CPAP



Tutti i pazienti PWS devono effettuare uno studio del sonno

La terapia con CPAP *(Continuous Positive Airway Pressure)* è il trattamento non invasivo per le apnee ostruttive nel sonno *(OSA)*

OSA possono anche essere corrette rimuovendo adenoidi e tonsille

Monitoraggio del paziente PWS in terapia con GH

- **Valutazione clinica e auxologica** *(ogni 6 mesi)*
- **Glicemia, insulinemia, HbA1c** *(ogni 6-12 mesi)*
- OGTT *(glicemia e insulina) (se obesi, età >10 aa, famil. DM)*
- **Ormoni tiroidei** ***(FT3, FT4, TSH)*** *ogni anno*
- **Assetto lipidico ed epatico** ***(ecografia epatica)*** *ogni anno*
- **IGF-1** *(ogni 4-6 mesi)*
- **Età ossea** (rx mano e polso sin) *(ogni anno)*
- **Polisonnografia** *(ogni anno) – valutare infezioni respiratorie*
- **Rx colonna vertebrale** *(ogni anno)*
- **Composizione corporea (DEXA)** *(ogni anno circa)*
- **Visita ortopedica, ORL, psicologica, cardiologica, dietista**

A. Goldstone et al, JCEM, 93 (11): 4183-4197, 2008
CL Deal et al, JCEM 98 (6): E1072-1087, 2013

Terapia con ormone della crescita nella sindrome di Prader-Willi

CONTROINDICAZIONI

- Obesità severa
- Malattie acute, particolarmente respiratorie
- Sleep apnee
- Diabete con complicanze *(retinopatia)*
- Intolleranza al glucosio, Diabete *(tipo 2) (?)*
- Neoplasie
- Ipersensibilità al farmaco
- Psicosi

Terapia con GH nella sindrome di Prader-Willi

EFFETTI POSITIVI

EFFETTI COLLATERALI

- **Intolleranza al glucosio, diabete *(tipo 2)***
- **Problemi respiratori**
- **Scoliosi e/o cifosi *(comparsa o peggioramento)***
- **Alterazioni della funzione tiroidea**
- **Scivolamento della testa dell'epifisi femorale**
- **Pseudotumor cerebri**
- **Comparsa di pubarca**
- **Possibile relazione tra assunzione di GH e alcune morti di bambini *(non dimostrata)***

Original Paper

HORMONE RESEARCH

Horm Res 2007;68:83–90
DOI: 10.1159/000100371

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Accepted: January 15, 2007
Published online: February 28, 2007

Effects of Growth Hormone Therapy on Glucose Metabolism and Insulin Sensitivity Indices in Prepubertal Children with Prader-Willi Syndrome

A. Crinò[a] G. Di Giorgio[a] M. Manco[b] G. Grugni[c] A. Maggioni[a]

[a]Paediatric and Autoimmune Endocrine Diseases Unit, and [b]Paediatric Liver Unit, Bambino Gesù Children's Hospital, Research Institute, Roma; [c]Italian Auxological Institute, Research Institute, Piancavallo, Verbania, Italy

In PWS it is necessary to consider the potential diabetogenic effect of GHT.

7-20% of PWS pts. develop DM2 or IGT, more frequently after the pubertal stage

Here, we focused our attention on changes induced by growth hormone replacement on glucose and insulin homeostasis in a paediatric population affected by PWS.

Conclusion

In conclusion, GHT could contribute to increase insulin resistance and to develop hyperinsulinaemia and IGT in PWS children, especially in obese subjects. Therefore, as already suggested, a close monitoring of glucose and insulin homeostasis with an annual OGTT, during as well as after GHT, is necessary in order to recognise precociously the occurrence of IGT or diabetes. However, an early dietary approach to maintain low BMI values is recommended in order to reduce the risk of these GHT side effects on glucose and insulin homeostasis. Nevertheless, further investigations are needed to better understand the complex mechanisms that lead to an impairment of glucose homeostasis in these patients.

DETERMINAZIONE 29 luglio 2010

Modifica alla nota AIFA 39 cui alla determinazione del 26 novembre 2009

NOTA 39 AIFA Ormone della crescita (somatotropina)

Altre condizioni dove il trattamento con rGH viene concesso in età pediatrica:

- sindrome di Turner citogeneticamente dimostrata;
- deficit staturale nell'insufficienza renale cronica;
- soggetti prepuberi affetti dalla sindrome di Prader Willi (PWS), geneticamente dimostrata, con Indice di Massa Corporea o Body Mass Index (BMI)<95°, normale funzionalità respiratoria, non affetti da sindrome dell'apnea ostruttiva nel sonno.

Al raggiungimento della statura definitiva non è più indicata la terapia con GH nelle seguenti patologie:

OMISSIS

Sindrome di Prader Willi

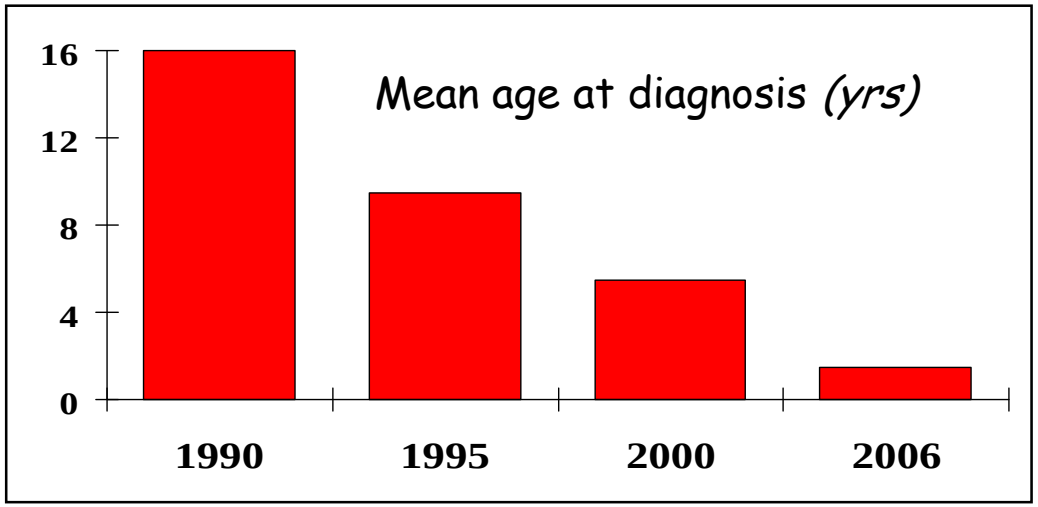
OMISSIS

Il test con GHRH + arginina viene ad oggi ritenuto l'alternativa di prima scelta e, dopo questo stimolo, un severo deficit di GH è dimostrato da un picco dei livelli circolanti di GH < 9 µg/L. Il rigoroso rispetto di tali criteri esclude la possibilità di un uso improprio o eccessivo del farmaco.

risposta di GH <19 µg/L dopo test farmacologico con GHRH + arginina

L'indicazione al trattamento nella PWS *(in età prepubere)* ha ottenuto l'autorizzazione da parte del ministero *(Nota AIFA 39)*

… come fermare la naturale evoluzione della PWS?



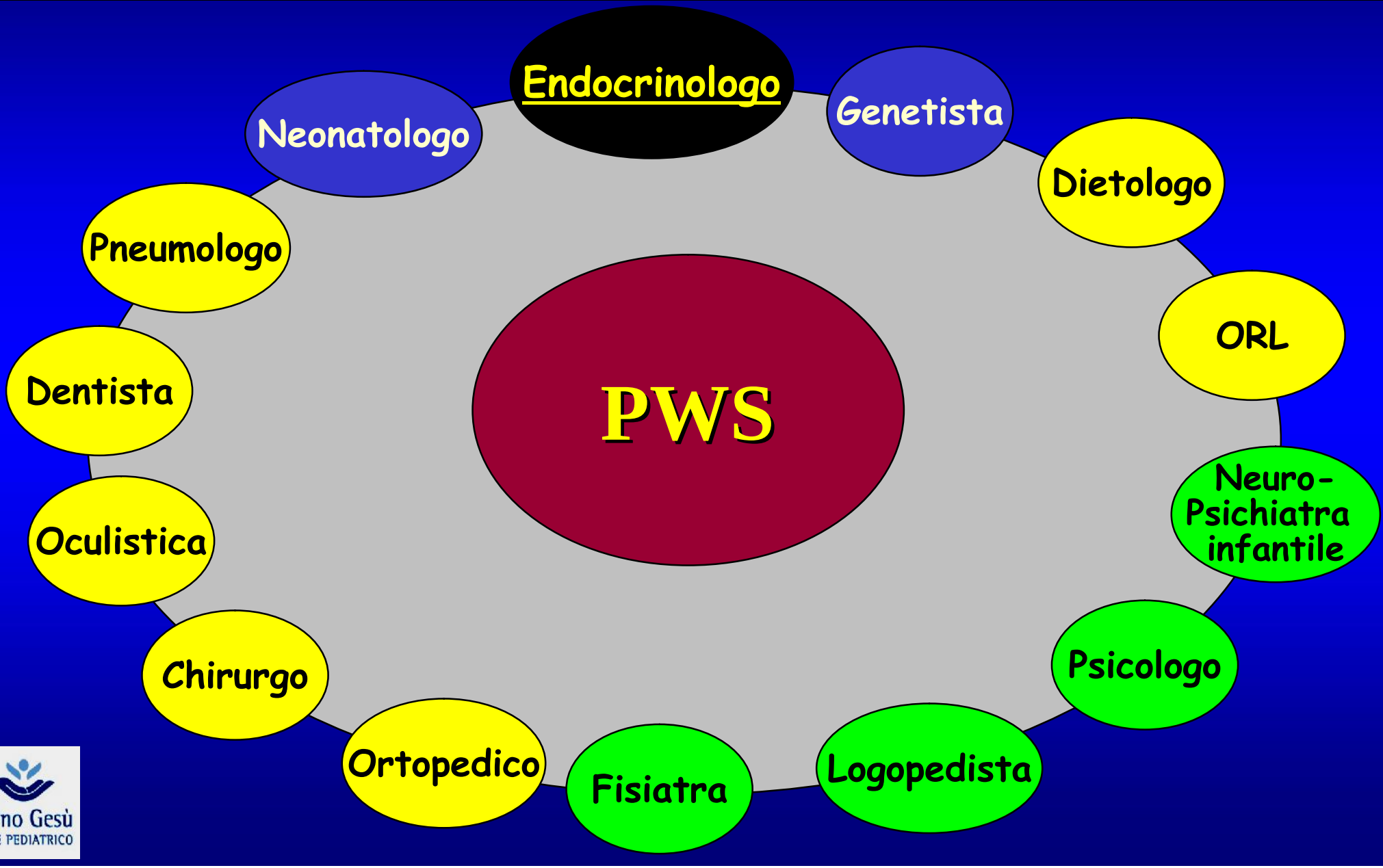
DIAGNOSI PRECOCE

Appropriati programmi terapeutici multidisciplinari

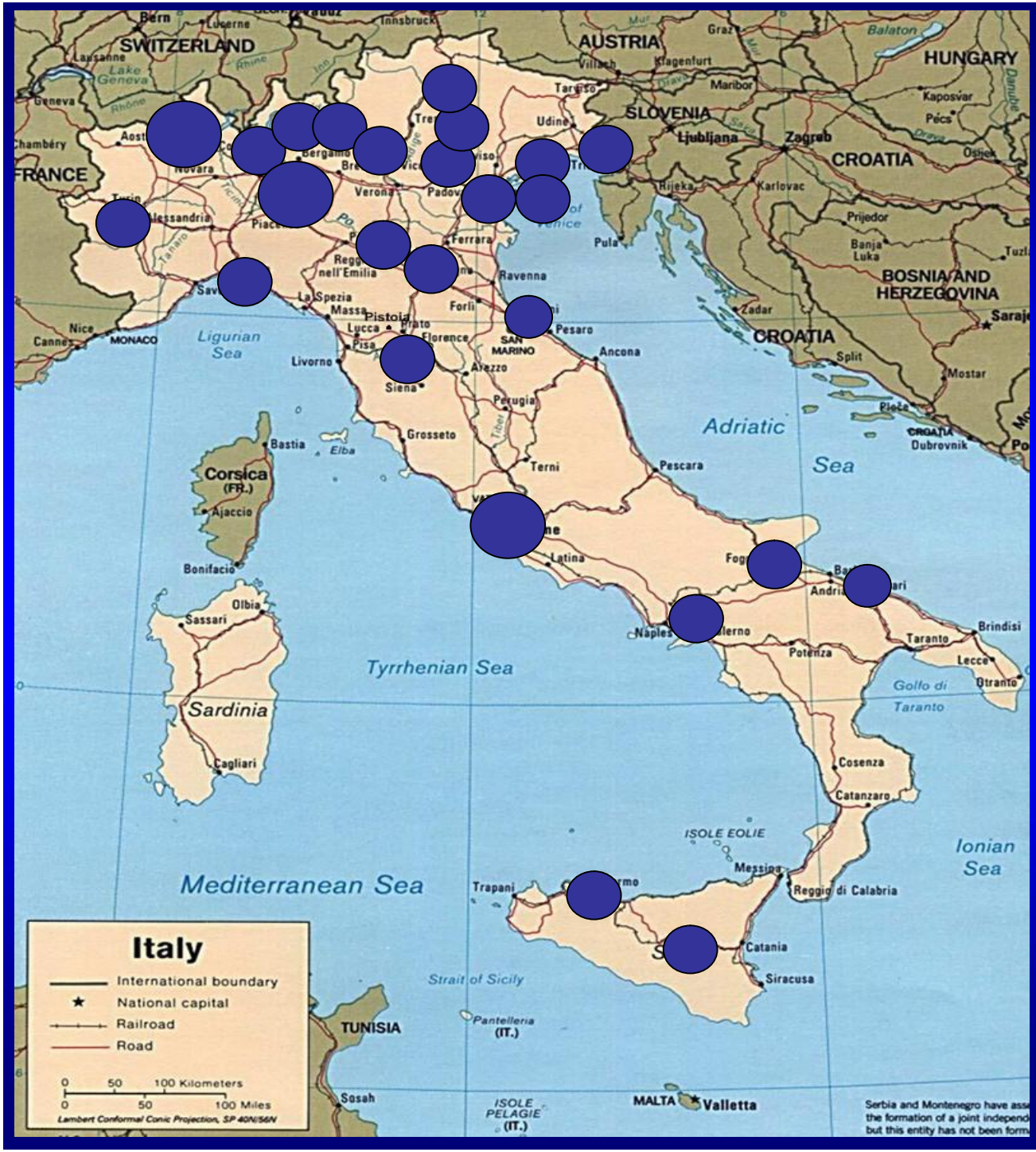
Educare parenti e caregivers.

PWS is a model showing that early diagnosis and comprehensive multidisciplinary approach, including GH treatment, prevents complications, optimises quality of life, and prolongs life-expectancy.

Assistenza Multidisciplinare nei pazienti con PWS



Bambino Gesù
OSPEDALE PEDIATRICO



Assistenza al paziente PWS in Italia

Lo studio nazionale italiano sulla PWS ha identificato 25 centri in grado di assicurare una idonea assistenza

Federazione Italiana Sindrome di Prader-Willi

Federazione Nazionale Sindrome di Prader-Willi

La sindrome di Prader-Willi
Raccomandazioni cliniche

In collaborazione con:

SIEDP - Gruppo di Studio delle Obesità Genetiche

A cura del Comitato Scientifico della Federazione Nazionale Sindrome di Prader-Willi - 2012
G. Chiumello, A. Crinò, A. Franzese, G. Grugni, C. Romano, A. Salvatoni

Ringrazio tutti Voi per la gentile attenzione

The Italian National Survey for Prader–Willi Syndrome:
An Epidemiologic Study

Graziano Grugni,[1*] Antonino Crinò,[2] Laura Bosio,[3] Andrea Corrias,[4] Marina Cuttini,[2] Teresa De Toni,[5] Eliana Di Battista,[5] Adriana Franzese,[6] Luigi Gargantini,[7] Nella Greggio,[8] Lorenzo Iughetti,[9] Chiara Livieri,[10] Arturo Naselli,[5] Claudio Pagano,[8] Giovanni Pozzan,[8] Letizia Ragusa,[11] Alessandro Salvatoni,[12] Giuliana Trifirò,[13] Luciano Beccaria,[14] Maria Bellizzi,[15] Jaele Bellone,[4] Amelia Brunani,[1] Marco Cappa,[2] Gabriella Caselli,[9] Valeria Cerioni,[3] Maurizio Delvecchio,[16] Daniela Giardino,[1] Francesco Iannì,[17] Luigi Memo,[18] Alba Pilotta,[19] Cristoforo Pomara,[20] Giorgio Radetti,[21] Michele Sacco,[22] Annarosa Sanzari,[23] Alessandro Sartorio,[1] Giorgio Tonini,[24] Roberto Vettor,[8] Federico Zaglia,[25] and Giuseppe Chiumello[3] *on behalf of the Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED)*

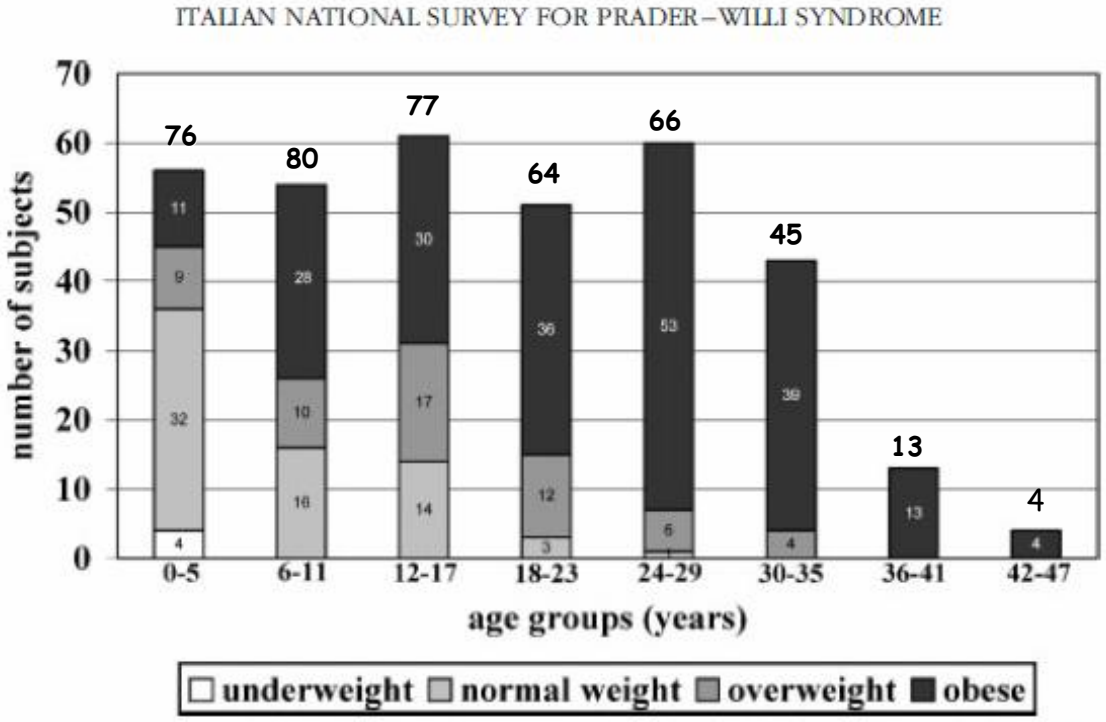


Fig. 1. Body weight status of Italian subjects with PWS in the different ages grouped in 6-year intervals.

425 soggetti PWS *(209 m,216 f)*

n. 233: <18 anni

n. 192: >18 anni

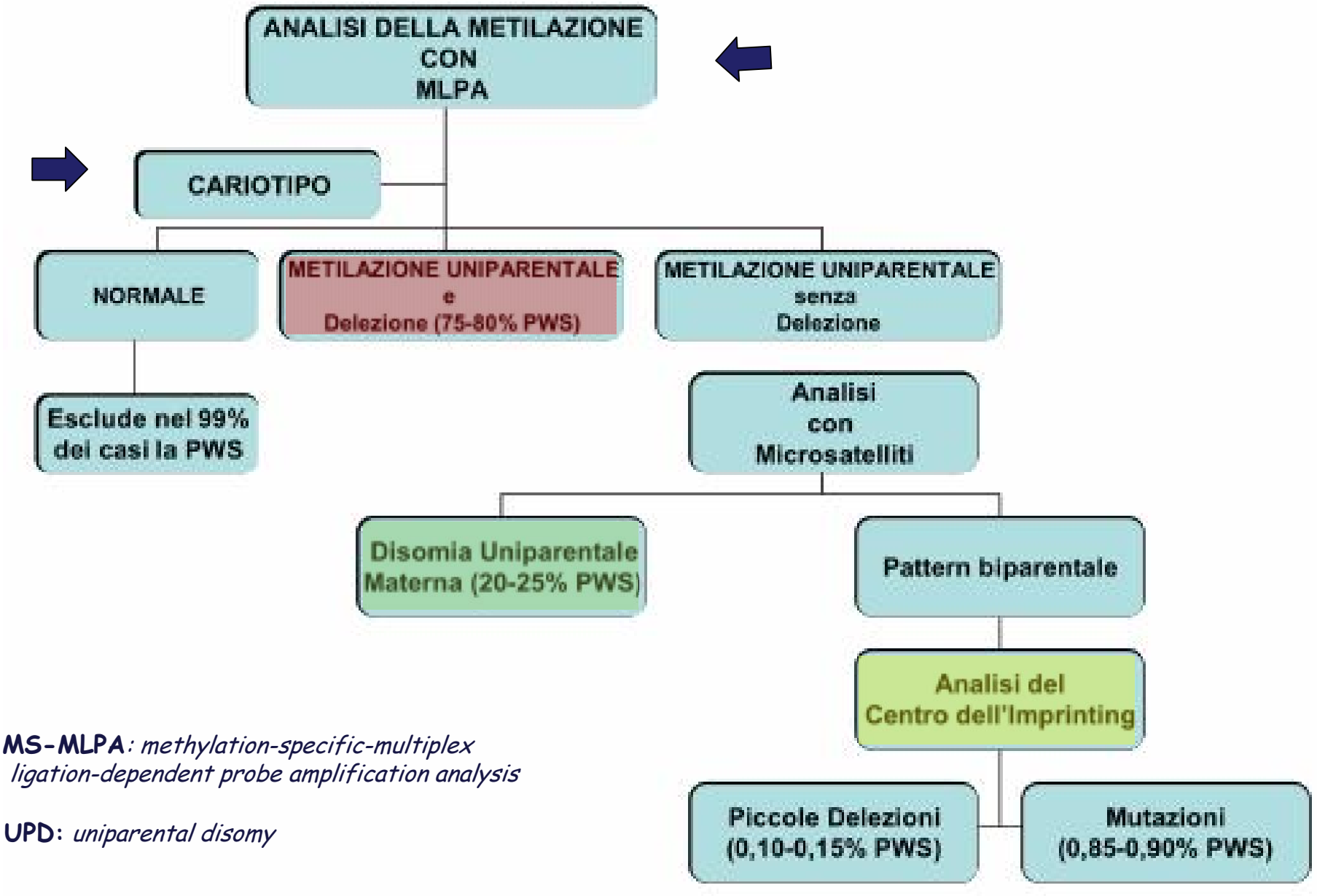
Deceduti n.18 *(6 f, 12 m)* ➡ **4.2%**

0.5-10 aa: n.4 decessi *(acidosi metabolica, broncopolmonite, problemi cardiaci, cause inspiegate)*

>16 aa: n.14 decessi *(broncopolmonite, problemi cardiaci e cardiorespiratori, perforazione gastrica)*

Grugni G et al.
Am J Med Genet A. 2008 146(7):861-72

Algoritmo per le indagini genetiche nella PWS



MS-MLPA: *methylation-specific-multiplex ligation-dependent probe amplification analysis*

UPD: *uniparental disomy*

American Journal of Medical Genetics Part A 146A:881–887 (2008)

Research Review

Review of 64 Cases of Death in Children With Prader–Willi Syndrome (PWS)

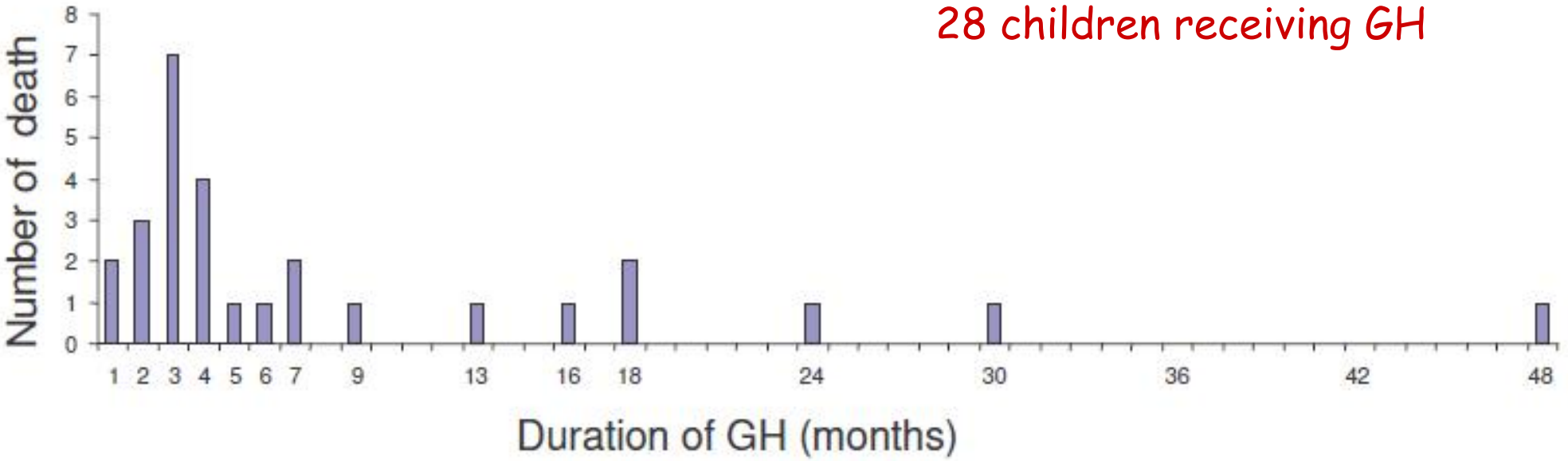
M. Tauber,[1]* G. Diene,[1] C. Molinas,[1] and M. Hébert[2]

[1]Division of Endocrinology, Genetics, Gynecology and Bone Diseases, Centre de Référence du Syndrome de Prader-Willi, Hôpital des Enfants, Toulouse Cedex 09, France

[2]Sudler & Hennessey, Boulogne-Billancourt, Paris, France

« Cluster » of deaths during the first months of GH

28 children receiving GH



Role of GH in deaths of children with PWS?

	With GH (n = 25)	Without GH (n = 14)	P value
Cause of death			
- Respiratory causes	17 (68%)	7 (50%)	
Infection	12 (48%)	6 (43%)	NS
Insufficiency	5 (20%)	1 (7%)	
- Gastroenteritis	0	2 (14%)	
- Sudden death	7 (28%)	4 (29%)	
- Accident	0	1 (7%)	
- Cardiac event	1 (4%)	0	
Median age in years (range)	6.4 (3–15.8)	3.5 (3–19)	p<0.0001
Gender ratio (male/female)	19/6	8/6	NS
Prevalence of obesity	82% (19/23)	62% (8/13)	NS
Prevalence of sleep apnoea	32% (8/25)	7% (1/14)	NS
Duration of GH treatment in months (range)	4 (0.43-48)		

M. Tauber, Am J Med Genet, 2008

JOURNAL OF ENDOCRINOLOGICAL INVESTIGATION 34:493-497, 2011

Growth Hormone secretion among adult patients with Prader-Willi syndrome due to different genetic subtypes.

G. Grugni[1], D. Giardino[2], A. Crinò[3], F. Malvestiti[2], L. Ballarati[2], G. Di Giorgio[3] and P. Marzullo[4,5].

Table 2: Stimulated GH levels and IGF-I (μg/l) values in Prader-Willi (PWS) patients and Obese controls. GH secretion is expressed either as GH peak (GHp) response (μg/l), area under the curve (AUC, μg/l/h) or AUC corrected for basal values (nAUC, μg/l/h) after GHRH+arginine administration.

	All PWS	del15q11-q13			UPD15	Obese controls
		All	TI	TII		
GHp	7.1±1.3[c]	9.1±1.8[d,e]	7.7±1.2[g]	9.6±2.6[f]	4.6±1.6[a]	15.7±2.9
GH AUC	411.3±83.1[c]	547.0±132.3[d,e]	424.2±88.8[h]	587.9±174.2[f]	241.6±71.7[a]	956.0±182.9
GH nAUC	387.5±80.4[b]	514.9±127.6[d,e]	393.4±88.8[h]	555.4±167.6[f]	228.3±71.6[a]	937.6±180.5
IGF-I	112.3±8.9[a]	104.8±11.3[c]	110.0±25.3[d]	102.7±12.8[c]	122.3±14.3[d]	196.9±26.4

del15q11-q13: deletion of chromosome 15; TI: type I deletion; TII: type II deletion; UPD15: uniparental maternal disomy of chromosome 15. [a]p<0.0001, [b]p<0.001, [c]p<0.005 and [d]p<0.05 versus Obese controls. [e]p<0.005, [f]p<0.01, [g]p<0.02 and [h]p<0.05 versus UPD15.

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ORIGINAL ARTICLE

Endocrine Care

Growth Hormone Therapy and Respiratory Disorders: Long-Term Follow-up in PWS Children

Jenny Berini, Valeria Spica Russotto, Paolo Castelnuovo, Stefania Di Candia, Luigi Gargantini, Graziano Grugni, Lorenzo Iughetti, Luigi Nespoli, Luana Nosetti, Giovanni Padoan, Alba Pilotta, Giuliana Trifirò, Giuseppe Chiumello, and Alessandro Salvatoni on behalf of the Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED)

Patients and Methods: We evaluated 75 children with genetically confirmed PWS, of whom 50 fulfilled the criteria and were admitted to our study. The patients were evaluated before treatment (time 0 [t0]), after 6 weeks (t1), after 6 months (t2), after 12 months (t3), and yearly (t4–t6) thereafter, for up to 4 years of GH therapy. The central apnea index, obstructive apnea hypopnea index (OAHI), respiratory disturbance index, and minimal SpO_2 were evaluated overnight using polysomnography. We evaluated the adenotonsillar size using a flexible fiberoptic endoscope.

Conclusion: Long-term GH treatment in patients with PWS is safe; however, we recommend annual polysomnography and adenotonsillar evaluation.

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Growth hormone secretory pattern in non-obese children and adolescents with Prader-Willi syndrome

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Analysis of integrated GH secretion (AUC) confirmed that the PWS group differed significantly from the control subjects (387.9±76.1 µg/L/h vs. 1498.1±56.2 µg/L/h, p<0.0001); the same result was obtained when the GH rise after arginine administration was expressed as nAUC (278.2±53.3 µg/L/h vs. 1443.6±52.5 µg/L/h, p<0.0001). PWS patients had an IGF-I SDS significantly lower than those found in control subjects (p<0.0001). Subnormal IGF-I values were present in 19 PWS individuals (82.6%) and two healthy controls (6.2%).

These findings are in agreement with the hypothesis that a complex derangement of hypothalamus-pituitary axis occurs in PWS.

23 PWS patients, 16 m, 7 f
Aged 2-14.3 yrs *(6.9±0.9 yrs)*

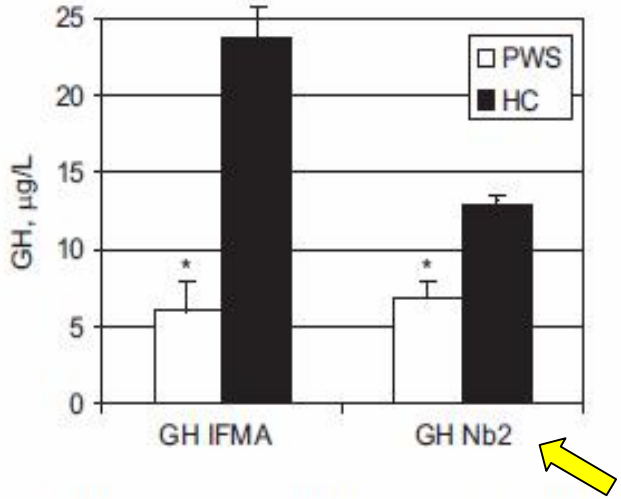
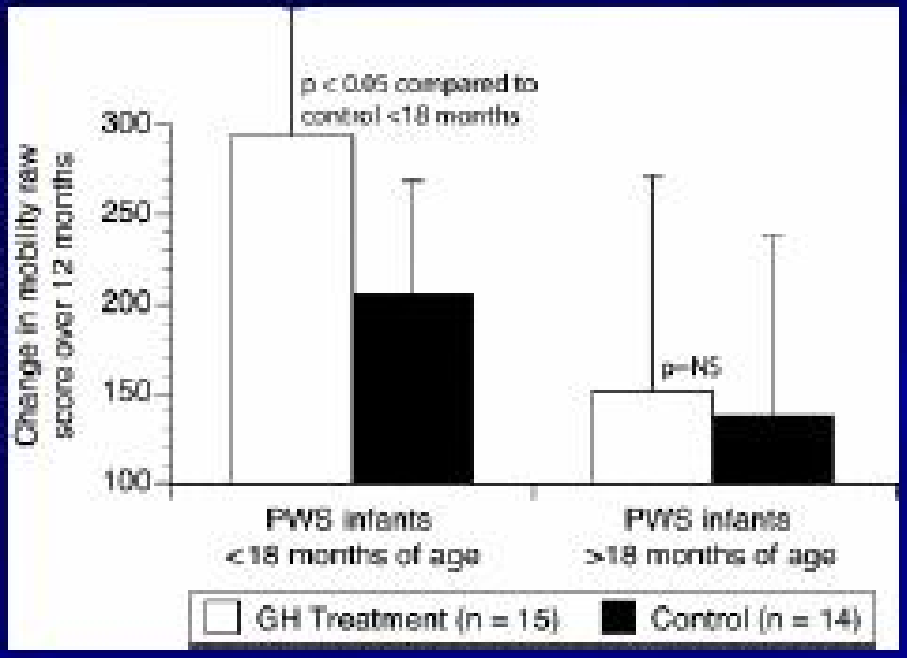


Figure 1 Growth hormone peak levels measured by IFMA and Nb2 cell assay in children and adolescents with Prader-Willi syndrome (PWS) and in healthy controls (HC). For significance: *p<0.0001 vs. HC.

GROWTH HORMONE IMPROVES MOBILITY AND BODY COMPOSITION IN INFANTS AND TODDLERS WITH PRADER-WILLI SYNDROME

AARON L. CARREL, MD, VICTORIA MOERCHEN, PHD, PT, SUSAN E. MYERS, MD, M. TRACY BEKX, MD, BARBARA Y. WHITMAN, PHD, AND DAVID B. ALLEN, MD



Age-related comparisons of change in mobility scores over 12 months revealed a significant effect for GH for infants who began GH before 18 months of age, an effect that was not observed in toddlers who began GH after 18 months of age.

Carrel et al, J Pediatr, 2004