



ABSTRACTS

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Guest Editor

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P2-d1-454 Obesity and Fat 1 ✓

The relation between central adrenal insufficiency and sleep related breathing disorders in children with Prader-Willi syndrome

Roderick de Lind van Wijngaarden¹; Barto Otten²; Koen Joosten³; Frank de Jong⁴; Fred Sweep⁵; Anita Hokken-Koelega⁶

¹Dutch Growth Research Foundation, Prader-Willi syndrome, Rotterdam, Netherlands; ²Radboud University Nijmegen Medical Center, Pediatric Endocrinology, Nijmegen, Netherlands; ³Erasmus University Medical Center Rotterdam, Pediatric Intensive Care, Rotterdam, Netherlands; ⁴Erasmus University Medical Center Rotterdam, Internal Medicine, Laboratory of Endocrinology, Rotterdam, Netherlands; ⁵Radboud University Nijmegen Medical Center, Chemical Endocrinology, Nijmegen, Netherlands; ⁶Erasmus University Medical Center Rotterdam, Pediatric Endocrinology, Rotterdam, Netherlands

The annual death rate of children with Prader-Willi syndrome (PWS) is high (3%). We reported an increased apnea-hypopnea-index in children with PWS, particularly during upper respiratory tract infection (URTI). It has been postulated that sleep apneas play a role in unsuspected deaths. Recently, however, we discovered that 60% of PWS patients suffer from central adrenal insufficiency (CAI) during stressful conditions. We, therefore, studied the relation between CAI and sleep apneas. Ten randomly selected PWS children were admitted for sleep monitoring during a metyrapone test (30 mg/kg at 2330h). ACTH and cortisol levels were measured at 0400h, 0600h and 0730h. CAI was diagnosed when ACTH levels were below 33 pmol/l at 0730h. We measured number and duration of central sleep apneas, desaturations, central-apnea-index and oxygenation-desaturation-index before and after metyrapone, until 0730h. Median (iqr) age was 7.3 (5.8-9.3) years. Six children had CAI. Median (iqr) central-apnea-index and oxygenation-desaturation-index were 4.2 (1.2-6.4) and 4.0 (3.4-5.1), respectively. There was no significant difference in sleep related breathing between children with CAI and those without. Central-apnea-index was significantly higher after 2330h (during the metyrapone test) than before ($p=0.02$). This was most likely due to difference in sleep stages, because no correlation was found with cortisol and ACTH levels. Our data do not show more central sleep apneas in PWS children with CAI who are in a healthy condition. However, we previously reported an increase in median (iqr) apnea-hypopnea-index during URTI from 5.7 (3.1-9.5) to 36.5 (18.1-39.5). Our data suggest that a combination of CAI and severely increased sleep apneas during acute illness may lead to a fatal cascade.

P1-d2-227 Obesity and Fat 2

Bioenterics intragastric balloon for treatment of morbid obesity in Prader-Willi syndrome: A long term study

Antonino Crino¹; Girolamo Di Giorgio¹; F De Peppo²; M. Germani²; C. Galli³; M.G. Ubertini⁴; S. Spera¹; M. Cuttini⁵; M. Cappa⁴; M. Rivosecchi²; G. Castelli Gattinara¹

¹Bambino Gesù Hospital, Research Institute, Paediatric and Autoimmune Endocrine Diseases Unit, Rome, Italy; ²Bambino Gesù Hospital, Research Institute, Paediatric Surgery Unit, Rome, Italy; ³Bambino Gesù Hospital, Research Institute, Anaesthesiology Unit, Rome, Italy; ⁴Bambino Gesù Hospital, Research Institute, Endocrinology Unit, Rome, Italy; ⁵Bambino Gesù Hospital, Research Institute, Epidemiology Unit, Rome, Italy

Obesity in Prader Willi Syndrome (PWS) is progressive and severe. A drastic body weight reduction is mandatory to reduce the risk of cardio-respiratory and metabolic complications. The insertion of a Bioenteric Intragastric Balloon (BIB) in the gastric cavity represents an effective alternative to the more complex and invasive bariatric surgery. Recently, we reported the risks and benefits of BIB for treatment of morbid obesity in 12 PWS patients during 6 months. The aim of this study was to assess long-term effects of BIB treatment. Five patients out of them (3M, 2F), aged 16.1±8.2 yrs (8.1-30.1 yrs), underwent multiple treatment with BIB. Two patients repeated the treatment twice, other two three times and one four times. We obtained excellent results in the two youngest patients. One was treated for the first time at 8.1 yrs (BMI: 44.6 kg/m²); 6 years later he stopped his fourth treatment with a BMI of 33.8 kg/m². The second patient (9.4 yrs) had a BMI of 39.1 kg/m²; at the end of his second treatment BMI was 23.6 kg/m². At 14.6 yrs, 2 yrs after last BIB, BMI was 29 kg/m². The third patient (12.4 yrs) inserted BIB three times in 3 years: starting BMI was 39.3 kg/m² and at the end of his third treatment, slightly increased to 40.2 kg/m². At 17.5 yrs, his BMI was 49.16 kg/m² and he underwent a bilio-pancreatic diversion. In the two oldest patients (20.6 and 30.1 yrs) only a slight BMI reduction was obtained with their first balloon and a BMI stabilization was observed during the subsequent treatments. During the free intervals or after treatment interruption BMI tended to increase in every patients. However, some complications occurred: acute gaseous gastric distension due to ingestion of a fizzy drink; balloon rupture; recurrent diarrhoea and aerophagia. This study shows that, when non-invasive pharmacological therapies fail, BIB may be effective to control body weight in PWS patients with morbid obesity, particularly if started in early childhood. Careful clinical follow-up and close collaboration with parents are crucial to avoid severe complications caused by unrestrained food intake despite BIB.

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Peripheral α -MSH in childhood obesity and craniopharyngioma

Christian L. Roth¹; Hermann Mueller²; Ursel Gebhardt²; Thomas Reinehr³; Pablo J. Enriori⁴; Michael A. Cowley⁴

¹University of Washington, Seattle Children's Hospital Research Institute, Seattle, United States; ²Klinikum Oldenburg, Pediatrics, Oldenburg, Germany; ³University of Witten/Herdecke, Vestische Children Hospital Datteln, Witten/Herdecke, Germany; ⁴Oregon Health and Science University, Div. of Neurosciences, National Primate Research C, Beaverton Oregon, United States

While the majority of energy homeostasis studies focus on central melanocortin action, peripheral effects of melanocortins and their receptors are not well established. Alpha-melanocyte stimulating hormone (α -MSH) are posttranslational products of the POMC prohormone and the pituitary pars intermedia lobe melanotrophs are considered to be the major source of circulating α -MSH in most mammals. Recent evidence shows that α -MSH plays a role in thermal regulation by increasing free fatty acid oxidation (FAO) and increase of glucose intake in skeletal muscle through the activation of MC5R by activation of the PKA-AMPK pathway. In this study, we aimed to investigate peripheral α -MSH levels in 1) children with simple obesity 2) lean children, 3) children with hypopituitarism, 4) patients with craniopharyngioma (CP) to learn more about the role of peripheral, human α -MSH in obesity and CP. Fasting serum α -MSH measured by radioimmunoassay with no cross-reactivity to ACTH. Furthermore we measured fasting leptin, insulin and glucose. Interestingly in patients with hypopituitarism or CP very low to zero α -MSH le-

vels were measured (healthy 26.6 fmol/ml vs hypopituitarism 8.4 fmol/ml vs craniopharyngioma 7.7 fmol/ml). Compared to patients with simple obesity, patients with CP significantly lower ($p < 0.001$) fasting serum α -MSH levels, but there were no significant differences of α -MSH levels in obese children compared to lean children. Low α -MSH levels in CP did not increase one hour after ingestion of a 500 kcal mixed liquid meal. CP patients had higher fasting insulin, insulin resistance index HOMA and leptin levels compared to patients with simple obesity and similar BMI. The low serum α -MSH levels in patient groups, which have low- or non-functioning pituitaries, verify that the pituitary is the critical source for circulating α -MSH. The very low α -MSH levels in CP can be explained by their pituitary or hypothalamic damage and might contribute to severe obesity associated with low thermogenesis.

Hyperghrelinemia precedes obesity in Prader-Willi syndrome

Gwenaëlle Diene¹; Eva Feigerlova¹; Françoise Conte-Auriol¹; Catherine Molinas¹; Isabelle Gennero²; Jean-Pierre Salles³; Catherine Arnaud⁴; Maïthé Tauber¹

¹Centre de référence du syndrome de Prader-Willi, Department of Endocrinology, Bone Diseases, Geneti, Toulouse, France; ²Laboratoire de Biochimie 3, Institut Fédératif de Biologie, Toulouse, France; ³INSERM U 563, Université Paul Sabatier, Toulouse, France; ⁴INSERM U 558, Université Paul Sabatier, Toulouse, France

Background: High plasma ghrelin levels have been reported in Prader-Willi syndrome (PWS) and could play a role in early-onset obesity. However, little is known about plasma ghrelin in these children during the first years of life characterized by a failure to thrive.

Objective: To investigate total plasma ghrelin levels in children with PWS and in controls from 2 months to 17 years. **Subjects and methods:** Forty children with PWS (24 boys 16 girls, median age 3.6 years [0.2 - 17.2 years], median BMI 0.3 Z-score [-4.0-+4.4]) were compared to 84 controls (57 boys 27 girls median age 4.2 years [0.3-17.1] median BMI 0.1 Z-score [-1.5-+1.9]). Children with PWS were then divided into 2 groups according to age and GH treatment.

Results: Median plasma ghrelin levels were significantly higher in children with PWS compared to controls at any age (568 vs. 173, $p < 0.0001$) and decreased with age in both groups ($p < 0.0001$). In the whole group of PWS, we found an inverse relationship between ghrelin and BMI Z-score ($p = 0.0032$), insulin ($p < 0.0001$), HOMA-IR ($p = 0.0002$), leptin ($p = 0.0027$) and lean mass ($p = 0.04$). Plasma ghrelin levels were significantly higher in children with PWS than in controls, both in the youngest children below 3 years who were not receiving GH (771 vs. 233 $p < 0.0001$) and in the children older than 3 years all of whom were treated with GH (428 vs. 159 $p < 0.0001$). In young children with PWS, we did not find any relationship between ghrelin and BMI Z-score, insulin, HOMA-IR and leptin.

Conclusions: Plasma ghrelin levels in children with PWS are elevated at any age, particularly during the first years of life, thus preceding the development of obesity.

P2-d1-332 GH Treatment 1

Cardiac dimensions in growth hormone-treated children and adolescents with Prader-Willi syndrome

Berthold P Hauffa¹; Kathrin Knaup¹; Nils Lehmann²; Ulrich Neudorf³; Katja Schaaf¹; Anna Grabensee¹; Bert Nagel⁴

¹Division of Pediatric Endocrinology and Diabetes, University Children's Hospital Essen, Essen, Germany; ²Inst for Med Informatics, Biometry & Epidemiology, University of Duisburg-Essen, Essen, Germany; ³Division of Pediatric Cardiology, University Children's Hospital Essen, Essen, Germany; ⁴Division of Pediatric Cardiology, Medical University Graz, Graz, Austria

Growth hormone (GH) status and GH therapy influence cardiac muscle mass and function. Patients with Prader-Willi syndrome (PWS) are at risk to develop secondary cardiac problems. Most PWS patients are GH-deficient, and GH therapy of PWS children is practiced in many countries. Few data exist on echocardiographic parameters under GH treatment in PWS.

Patients and Methods: We performed M-mode echocardiographic examinations (Phillips SONOS 5500) in 19 children (age 7.0±3.7 yrs [mean±1 SD]) with PWS before and after 26.5±10.6 months of GH therapy (0.035 mg/kg/d).

Data were compared to those of 19 control children (age 9.0±3.7 yrs) treated with GH (0.035-0.045 mg/kg/d) for other reasons over 14.3±4.7 months. End diastolic interventricular septal thickness (IVSd), end diastolic left ventricular dimension (LVEDD), right ventricular end diastolic dimension (RVEDD), end diastolic left ventricular posterior wall thickness (LVPWd), end systolic interventricular septal thickness (IVSs), aortic diameter (AOD), body mass index (BMI) and IGF-I and IGFBP-3 serum concentrations were measured.

Results: Pretreatment BMI-SDS were elevated in PWS patients over controls (1.6 vs. -0.1, $p < 0.0001$), decreasing significantly with GH therapy (-0.5, $p = 0.001$ vs. -0.1, $p = 0.25$). GH therapy increased IGF-I-SDS in all groups. The group means of all echocardiographic parameters were in the normal range in PWS patients and controls, before and under GH therapy. The increases with GH of IGF-I and of IVSd correlated positively ($r = 0.46$, $p = 0.05$) in controls, but not in PWS patients. With GH treatment, LVEDD increased more in PWS patients (+1.26 SD) than in controls (+0.44 SD) ($p = 0.045$). However, PWS patients were treated longer.

Conclusion: GH therapy induced moderate changes of echocardiographic dimensions within the normal range for most PWS children. Some of these changes may reflect the GH metabolic effects on IGF-I, so that regular echocardiographic assessment should be recommended at least for PWS children with higher IGF-I concentrations under GH therapy.

Ten years of growth hormone therapy in patients with Prader-Willi syndrome

Ilkka Sipilä¹; Heikki Hietanen²; Anna-Mari Viita³

¹Helsinki University, Pediatrics, Helsinki, Finland; ²Vita-Terveys, Clinical Physiology, Helsinki, Finland; ³Oy Eli Lilly Finland, Clinical Research, Vantaa, Finland

Twenty subjects with Prader-Willi Syndrome (PWS) were treated with growth hormone (GH, Humatrope®) for one year in a clinical study between 1996 and 1998 (GH Dose 0.1 IU/kg/d). After the initial study these patients were treated in their own hospital districts according to local clinical practice with various GH treatment regimens. To assess the long term effects of GH on body composition, weight and safety, a follow-up study with one study visit was conducted, when 19 subjects out of the 20 in the original study underwent a clinical examination, laboratory sampling, DEXA measurement and a limited sleep polygraph. All 20 subjects, 14 male and 6 female, were contacted. One female subject refused to participate. Adult height was achieved in 9 males (age 21.0 ± 1.8 y, mean ± SD) and 4 females (19.3 ± 3.6 y) and was markedly greater (176.1 ± 4.6 cm and 156.4 ± 8.9 cm, respectively) than in historical controls. Seven subjects were still on GH. The height SDS in the whole group was -0.3 ± 1.1 (range -3.2 to +1.3). The weight for height was 182.8 ± 39.1 % (range 113 to 244 %) and only 1 had normal weight (<120%). BMI was 34.9 ± 7.8 kg/m² in males and 36.7 ± 7.1 kg/m² in females. The total body fat % was 50.4 ± 6.0 % (range 36.5 to 59.9 %). We did not see any significant effect of GH on the prevention of being overweight, although an increasing dose appeared related to a lower total body fat % (r=-0.49, p=0.03). All subjects, for whom DEXA scans were performed (n=17), had a normal bone mineral density. A sleep polygraph was obtained from 18 subjects and was considered normal in 7 and slightly abnormal in 9 subjects. A markedly abnormal result, indicating sleep apnea, was found in 2 subjects. No significant differences in HbA1c, plasma glucose, or insulin levels between GH-users and non-users were observed. No adverse events were reported as related to GH treatment by the study investigator. We conclude that long-term GH treatment in patients with PWS is safe, and improves adult height and body composition.

P2-d1-310 GH Physiology

Ghrelin and leptin levels in prepubertal children with short stature with and without growth hormone deficiency (GHD): Relationship with growth hormone (GH) and insulin growth factor -I (IGF-I)

Charilaos Stylianou¹; Dimitrios Farmakiotis²; Georgios Koliakos³; Assimina Galli-Tsinopoulou¹

¹Medical School, Aristotle University Thessaloniki, 4th Dep. of Pediatrics, Thessaloniki, Greece; ²Medical School, Aristotle University Thessaloniki, Division of Endocrinology and Human Reproduction, Thessaloniki, Greece; ³Medical School, Aristotle University Thessaloniki, Department of Biochemistry, Thessaloniki, Greece

Introduction: The influence of GH sufficiency in the levels of ghrelin and leptin has not yet been clarified.

Aim: To compare fasting ghrelin and leptin levels between children with short stature (SS) (with and without GHD) and to investigate correlations between ghrelin, leptin, GH and IGF-I in the studied groups.

Patients And Methods: Twenty prepubertal children with SS were enrolled. Thyroid, kidney and liver functions were normal, celiac disease was excluded. MRI image of pituitary gland was normal. All SS-children underwent two standard GH stimulation tests. 10/20 were found to have GHD. 15 children with normal height served as the control group. Fasting ghrelin, leptin, GH and IGF-I levels were determined. Student's independent t-test, Mann-Whitney U-test were applied for statistical analysis.

Results: Anthropometric and hormonal features of the children studied: mean ± SE

	non-GHD	GHD	Controls	P
Gender (M/F)	8/2	5/5	8/7	NS
Age (yrs)	9.01±2.93	9.80±2.29	7.99±2.18	NS
Height (cm)	123.00±17.84†	128.05±13.08†	131.33±14.36*	0.000
Weight (kg)	31.07±17.61	34.40±14.42	30.13±8.91	NS
BMI (kg/m ²)	19.71±7.26	20.63±3.80	19.97±3.14	NS
GH (ng/ml)	3.26±3.25	1.67±2.13†	4.33±2.05*	0.022
IGF-I (ng/ml)	403.1±357.3	279.7±275.6†	563.3±159.9*	0.026
Leptin (ng/ml)	9.53±8.52	12.04±9.98	9.82±7.23	NS

Ghrelin levels were lower in children with SS with or without GH deficiency, compared to the controls (p<0,001). No significant difference was observed between the two groups with SS. No statistical significance differences were observed between the three groups for leptin levels.

Conclusions: Ghrelin levels are lower in prepubertal children with SS, independently of GH sufficiency or not.

P2-d3-733 Reproductive Endocrinology 2

Aromatase inhibitors resolve hypogonadotropic hypogonadism and significantly reduce body weight in Prader-Willi syndrome

Dimitrios T. Papadimitriou¹; A Fretzayas²; Polyxeni Nicolaidou²; Anastasios Papadimitriou¹

¹Attikon University Hospital, Pediatric Endocrinology, Athens, Greece;

²Attikon University Hospital, Pediatrics, Athens, Greece

Prader-Willi syndrome (PWS) is a genetic disorder characterized by dysmorphic features, obesity, hypotonia, mental retardation, often premature adrenarche and hypogonadism. The type of hypogonadism in PWS, central or peripheral, remains unclear as recent studies support a combined hypothalamic and peripheral mechanism, whilst other recent reports show an intact mini-puberty in male infants with PWS. We evaluated a boy with PWS at the age of 13.2 yrs. He presented since the age of 5 yrs premature adrenarche and morbid obesity. Genetic studies showed maternal uniparental disomy of chromosome 15q11-q13. He measured 144.5 cm (-1.73 SDS), weighed 72.9 Kg (+2.19 SDS) -unchanged the last 3 yrs-, his BMI was 34.9 Kg/m² (+3.28 SDS) and his bone age 15.8 yrs. Predicted adult height was 147.9 cm with a target height of 179 cm. At presentation he was hypogonadic with testes barely palpable (both < 1 ml), but with normal penile length for pubertal stage. He showed normal response of 17-OH-progesterone to ACTH test, no response to LHRH stimulation (peak LH 0.8 and FSH 1.2 mIU/ml), complete GH deficiency and low IGF-1 levels, high estradiol (E2) 47 pg/ml and low testosterone 0.5 ng/ml. Aiming to improve -even slightly- final height by slowing down bone age maturation while awaiting approval for hGH treatment, he was put on anastrozole (Arimidex®) 1 mg/day p.o. After 8 months he grew 1.5 cm and gained 1.1 cm in predicted adult height as his bone age advanced only by 0.2 yrs. He lost 5.9 Kg (8%) of body weight without any dietary change, testicular volume increased to 6 ml bilaterally, E2 levels decreased to 15 pg/ml, whereas basal (8:00am) LH, FSH and testosterone levels increased to 11, 10.5 mIU/ml and 5.6 ng/ml respectively. These data suggest that aromatase inhibitors may resolve hypogonadotropic hypogonadism in PWS supporting a peripheral rather than a central mechanism, involving high E2 levels. Normalization of E2 may also be related to the striking improvement in body weight.

A case of PRES (posterior reversible encephalopathy syndrome) in a patient with Prader Willy syndrome

Rosalba Bergamaschi¹; Sara Forti²; Rita Sciutti²; Bruno Bernardi³; Ercole Galassi⁴; Paolo Montanari²; Mino Zucchelli⁴; Alessandro Cicognani¹

¹Department of Pediatrics, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; ²Department of Radiology, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; ³Department of Pediatric Neuroradiology, Bellaria Hospital, Bologna, Bologna, Italy; ⁴Department of Pediatric Neurosurgery, Bellaria Hospital, Bologna, Bologna, Italy

A 7 years-old-boy, with Prader Willy Syndrome (PWS), was admitted to Emergency Room for asthenia and a headache. When the patient was three years old, since he had growth hormone deficiency, started therapy with GH. After 5 months a echocardiogram disclosed the presence of a dilatative cardiomyopathy, with mitral-aortic insufficiency and arterious hypertension, so he stopped GH therapy and started antihypertensive therapy. For the worsening of his headache with severe hypertension, ultrasound evaluation of the urinary tract showed a left kidney smaller than normal with a scarce differentiation between renal cortex and medulla. An URO-MR showed renal medulla's cystic dysplasia; the urethra-cistography didn't find neither bladder-urethral reflux nor alterations in the bladder's wall. Then a brain MR was performed and it showed multiple areas of T2 hyperintensity and corresponding T1 hypointensity, involving both of the cerebral hemispheres. Abnormal signal intensity was prevalingly subcortical but also involved the cortex regionally. On diffusion-weighted (DWI) images, the signal abnormalities showed absence of restricted diffusion, consistent with vasogenic, rather than cytotoxic edema. The cerebellum was less affected but a downward displacement of the cerebellar tonsils into the foramen magnum was evident (acquired Chiari I, due to intracranial hypertension). The child underwent a suboccipital decompression. The post-operative course was characterized by very high arterious hypertension which got normal after 10 days of therapy. The follow up MR studies showed the complete resolution of imaging abnormalities. Clinical and imaging

manifestations reversibility confirmed the diagnosis of PRES secondary to acute high blood pressure. This is the first case of PRES in a patient with PWS. The hypertrophic-dilatative cardiomyopathy, the arterious hypertension and the renal cystic dysplasia strongly suggested this hypothesis, confirmed by reversible characteristic MR findings.

Metabolic syndrome in children and adolescents with Prader-Willi syndrome: Preliminary results

Graziano Grugni¹; Marco Cappa²; Andrea Corrias³; Antonino Crinò⁴; Luigi Gargantini⁵; Lorenzo Iughetti⁶; Letizia Ragusa⁷; Alessandro Salvatori⁸; Paolo Brambilla⁹

¹Istituto Auxologico Italiano Foundation, Division of Auxology, Verbania, Italy; ²Bambino Gesù Children's Hospital, Department of Paediatric Endocrinology, Rome, Italy; ³Regina Margherita Hospital, Department of Paediatric Endocrinology, Turin, Italy; ⁴Bambino Gesù Children's Hospital, Paediatric and Autoimmune Endocrine Diseases Unit, Palidoro-Rome, Italy; ⁵Civic Hospital, Department of Paediatrics, Treviso (BG), Italy; ⁶University of Modena and Reggio Emilia, Department of Paediatrics, Modena, Italy; ⁷Oasi Maria S.S., Research Institute, Department of Paediatric Endocrinology, Troina (EN), Italy; ⁸University of Insubria, Department of Paediatrics, Varese, Italy; ⁹ASL Provincia di Milano 2, Paediatrician, Milan, Italy

Prader-Willi syndrome (PWS) is the most common recognised genetic form of obesity. Adult patients with PWS die prematurely from complications conventionally related to obesity, such as type 2 diabetes mellitus (DMT2) and cardiovascular disease (CVD). The metabolic syndrome (MetS) is a strong risk factor for DMT2 and atherosclerotic CVD. There is evidence that the development of MetS has its origin in children and adolescents, suggesting that early identification and treatment of MetS may be helpful to improve morbidity and mortality of PWS adults. The objective of this study was to estimate the prevalence of MetS among children and adolescents with PWS. Thirty-nine subjects with genetically confirmed PWS, 15 males and 24 females, aged 2.4-17.6 yr, were studied. Height and weight were measured by using standardized equipment. Growth Analyser 3 was adopted to calculate BMI-SDS values. Blood pressure (BP) was measured in each subject at least three times at 5-min intervals, and the mean values of three tests were used in analyses. Biochemical testing included measurements of fasting glucose, triglycerides, HDL cholesterol levels as well as glucose levels after Oral Glucose Tolerance Test. According to Weiss et al. (N Engl J Med 2004), we define MetS as having at least 3 of the following: BMI-SDS > 2, high systolic BP or diastolic BP, high triglycerides, low HDL and impaired glucose tolerance. The MetS component cut-points were developed with data from Italian Consensus on Childhood and Adolescence Obesity (2006). In our sample, 69.2% of subjects (n=27) had 1 or more abnormalities of the MetS, whereas 33.3% (n=13) had 2 or more. The overall prevalence of the MetS was 10.2% (n=4). The distribution of each element of the MetS was the following: obesity 56.4%, elevated BP 30.7%, high triglycerides 20.5%, low HDL 0%, IGT/DMT2 7.7%. Our findings demonstrate that cardiovascular risk factors are common in young PWS subjects, suggesting a relationship with the decreased life expectancy observed during adulthood.