

## PWS publications January to March 2022

### PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1<sup>st</sup> January and end of March 2022 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health.

This list has been compiled by Joyce Whittington and by members of the IPWSO Scientific Advisory Committee. If there are papers that you think should have been included please let Joyce Whittington know ([jew1000@cam.ac.uk](mailto:jew1000@cam.ac.uk) tel. +44 (0)1223 465266).

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# PWS publications 1<sup>st</sup> Jan to 31<sup>st</sup> Mar 2022

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### General PWS and families

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Anthony Holland , Katie Manning , Joyce Whittington. The paradox of Prader-Willi syndrome revisited: Making sense of the phenotype. *EBioMedicine.* 2022 Mar 19;78:103952. Online ahead of print.

Rishi Raj , Douglas Owen , Lakshmi Kannan , Ummerubab Syeda. Polypharmacy in a Patient With Intellectual and Developmental Disabilities. *Cureus.* 2022 Feb 8;14(2):e22019. eCollection 2022 Feb.

Alexandre Slowetzky Amaro , Daniela Andrea Rubin , Maria Cristina Triguero Veloz Teixeira , Arcenio José Ferreira Jr , Graciele Massoli Rodrigues , Luiz Renato Rodrigues Carreiro. Health Problems in Individuals With PWS Are Associated With Lower Quality of Life for Their Parents: A Snapshot in the Brazilian Population. *Front Pediatr.* 2022 Feb 15;10:746311. eCollection 2022.

J E Whittington , A J Holland , D J Driscoll , N Hodebeck-Stuntebeck , A Hctor. The presentation, course and outcome of COVID-19 infection in people with Prader-Willi syndrome: unexpected findings from an international survey. *Orphanet J Rare Dis.* 2022 Feb 21;17(1):69.

Lionne N Grootjen , Nathalie E M Uyl , Inge A L P van Beijsterveldt , Layla Damen , Gerthe F Kerkhof , Anita C S Hokken-Koelega. Prenatal and Neonatal Characteristics of Children with Prader-Willi Syndrome. *J Clin Med.* 2022 Jan 28;11(3):679.

Charlotte Höybye , Maithé Tauber. Approach to the patient with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2022 Feb 12;dgac082. Online ahead of print.

Nicole Campbell , Scott Van Zant , Joyce Lammers. Multifactorial influences on successful health outcomes for an adolescent with Prader-Willi syndrome: a qualitative case study. *Physiother Theory Pract.* 2022 Jan 31;1-9. Online ahead of print.

### Genetics and brain imaging

Tomohiro Okuda , Masaharu Moroto , Toshiyuki Yamamoto. Noninvasive prenatal testing suggesting an abnormality in chromosome 15 confirmed to be a case of Prader-Willi syndrome caused by trisomy rescue in the neonatal period. *J Obstet Gynaecol Res.* 2022 Mar 23. Online ahead of print

Kenichi Yamada , Masaki Watanabe , Kiyotaka Suzuki. Differential volume reductions in the subcortical, limbic, and brainstem structures associated with behavior in Prader-Willi syndrome. *Sci Rep.* 2022 Mar 23;12(1):4978.

Guanghan Jia , Yazhou Cui , Liang Shi , Jing Luan , Jing Wang , Jingxiang Han. Generation of a transgene-free induced pluripotent stem cell line (SMBCi011-A) from a patient with Prader-Willi syndrome. *Stem Cell Res.* 2022 Feb 12;60:102695. Online ahead of prin

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Marta Drabik , Andrzej Lewiński , Renata Stawerska. Management of Prader-Labhart-Willi syndrome in children and in adults, with particular emphasis on the treatment with recombinant human growth hormone. *Pediatr Endocrinol Diabetes Metab*. 2022;28(1):64-74.

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Su Jin Kim , Sung Yoon Cho , Dong-Kyu Jin. Prader-Willi syndrome: an update on obesity and endocrine problems. *Ann Pediatr Endocrinol Metab* 2021 Dec;26(4):227-236. Epub 2021 Dec 31.

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Gisela Vasconcelos , Jo S Stenehjem , Stefan Axelsson , Ronnaug Saeves. Craniofacial and dentoalveolar morphology in individuals with Prader-Willi syndrome: a case-control study. *Orphanet J Rare Dis.* 2022 Feb 22;17(1):77.

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PMID: 35079744 PMC8749009 DOI: 10.34197/ats-scholar.2021-0025PE

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## **Behaviour**

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Anthony Holland, Katie Manning. t-VNS to treat disorders of behaviour in Prader-Willi Syndrome and in people with other neurodevelopmental conditions. *Auton Neurosci*. 2022 Feb 12;239:102955. Online ahead of print.

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Jenny Downs, A Marie Blackmore, Wai Chen, Gillian M Nixon, Catherine S Choong. Strengths and challenging behaviors in children and adolescents with Prader-Willi syndrome: Two sides to the coin. *Am J Med Genet A*. 2022 Jan 29. Online ahead of print.

Sung Yoon Cho, Danbee Kang, Minji Im, Aram Yang, Min-Sun Kim, Jiyeon Kim, , Eun Kyung Kwon, Eu Jin Choi, Sunju Han, Young Ah Park, Min Jung Kwak, Youngha Kim, Juhee Cho, Dong-Kyu Jin. *Epidemiol Health*. 2022 Jan 10;e2022014. Online ahead of print

### **Cognition and mental health**

Emily Shelkowitz, Marie G Gantz, Ty A Ridenour, Ann O Scheimann, Theresa Strong, Jessica Bohonowych, Jessica Duis. Neuropsychiatric features of Prader-Willi syndrome. *Am J Med Genet A*. 2022 Jan 30. Online ahead of print.

## Abstracts

### General PWS and families

Stefano Lazzer Filippo Vaccari , Mattia D'Allewa , Giorgio Bedogni , Diana Caroli , Graziano Grugni , Alessandro Sartorio. Predictive factors of responsiveness to a body weight reduction program in Prader-Willi patients at 6 years of follow-up. *Sci Rep.* 2022 Mar 25;12(1):5182.

**Abstract** Prader-Willi syndrome (PWS), a multisystemic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region, is characterized by hyperphagia and childhood-onset morbid obesity. A retrospective cohort study of 60 PWS patients, 38 females and 22 males, undergoing a 6-year rehabilitation program was analysed. Mean age at the time of first admission was  $27 \pm 7$  years, body weight (BW) was  $97 \text{ kg} \pm 29 \text{ kg}$  and height was  $1.53 \pm 0.09 \text{ m}$ . Twenty-four patients (40%) showed BW loss after 6 years of follow-up, seventeen (28%) remained stable and nineteen (32%) gained BW. Responsiveness in term of BW reduction was less frequent in patients with the UPD karyotype, karyotype del15 being more frequent among responsive patients. Furthermore, responsive PWS subjects had a higher BMI ( $47 \text{ vs. } 36 \text{ kg/m}^2$ ), waist ( $123 \text{ vs. } 106 \text{ cm}$ ) and hip ( $136 \text{ vs. } 118 \text{ cm}$ ) circumferences than non-responsive at the time of first hospitalization. Baseline body composition and metabolic parameters did not differentiate between responsive and non-responsive patients. Given the rarity of PWS and relative lack of studies, these results can be considered relevant because based on a relatively large number of PWS patients followed up for a long term period.

PMID: 35338212 DOI: 10.1038/s41598-022-09096-x

Anthony Holland , Katie Manning , Joyce Whittington. The paradox of Prader-Willi syndrome revisited: Making sense of the phenotype. *EBioMedicine.* 2022 Mar 19;78:103952. Online ahead of print.

**Abstract** Prader-Willi syndrome arises as a consequence of absent paternal copies of maternally imprinted genes at 15q11-13. Such gender-of-origin imprinted genes are expressed in the brain and also in mammalian placenta where paternally expressed imprinted genes drive foetal nutritional demand. We hypothesise that the PWS phenotype is the result of the genotype impacting two pathways: first, directly on brain development and secondly, on placental nutritional pathways that results in its down-regulation and relative foetal starvation. The early PWS phenotype establishes the basis for the later characteristic phenotype. Hyperphagia. and other phenotypic characteristics arise as a consequence of impaired hypothalamic development. Hypothalamic feeding pathways become set in a state indicative of starvation, with a high satiety threshold and a dysfunctional neurophysiological state due to incorrect representations of reward needs, based on inputs that indicate a false requirement for food. Our hypotheses, if confirmed, would lead to novel and effective interventions. Keywords: Foetal nutritional pathways; Gender specific genomic imprinting; Hyperphagia; Prader-Willi syndrome.

PMID: 35316681 PMCID: PMC8943243 DOI: 10.1016/j.ebiom.2022.103952

Rishi Raj , Douglas Owen , Lakshmi Kannan , Ummerubab Syeda. Polypharmacy in a Patient With Intellectual and Developmental Disabilities. *Cureus.* 2022 Feb 8;14(2):e22019. eCollection 2022 Feb.

**Abstract** Prader-Willi syndrome (PWS) is an uncommon condition and its clinical manifestation in adulthood includes central obesity, hypogonadism, osteoporosis, cardiovascular disease, diabetes mellitus, and sleep apnea. These patients often have mild to moderate intellectual disability and are dependent upon their caregiver for healthcare needs. Hence, they may be at increased risk of polypharmacy-related complications, if there is poor communication between healthcare providers and caregivers. We present a case of a 26-year-old adult with PWS and mild to moderate intellectual disability, who was found to have acute kidney injury resulting from drug interaction between multiple nephrotoxic medications. Our case report highlights the importance of continuity of care with primary care providers, especially in patients with intellectual and developmental disabilities (IDD).

Keywords: acute kidney injury; drugs; intellectual and developmental disabilities; polypharmacy; prader-willi syndrome.

PMID: 35282537 PMID: PMC8908801 DOI: 10.7759/cureus.22019

Alexandre Slowetzky Amaro , Daniela Andrea Rubin , Maria Cristina Triguero Veloz Teixeira , Arcenio José Ferreira Jr , Graciele Massoli Rodrigues , Luiz Renato Rodrigues Carreiro. Health Problems in Individuals With PWS Are Associated With Lower Quality of Life for Their Parents: A Snapshot in the Brazilian Population. *Front Pediatr.* 2022 Feb 15;10:746311. eCollection 2022.

**Abstract** Prader-Willi syndrome (PWS) is a complex genetic disorder requiring interdisciplinary team monitoring and intensive care by parents. So far there is little information on people with PWS in Brazil. Our aim was to describe health problems and treatments used by people with PWS in Brazil and their relationship to their parents' quality of life. Parents answered questionnaires about their child's medical and exercise history, behavior problems, sociodemographic characteristics, and their own quality of life. Results: The responses of the participants showed similar health problems as in other countries. Anxiety and tantrums were the behavioral problems most commonly cited by parents. Parents of people with PWS had lower scores in respect of quality of life than the Brazilian population. Behavioral problems in individuals with PWS were negatively associated with their parents' quality of life. Behavioral and medical conditions in the children were associated with reduced quality of life in the parents. We conclude that health care should not only be directed toward those with PWS, but also their parents.

Keywords: Prader-Willi syndrome; behavior problems; obesity; quality of life; treatment.

PMID: 35242723 PMID: PMC8885721 DOI: 10.3389/fped.2022.746311

J E Whittington , A J Holland , D J Driscoll , N Hodebeck-Stuntebeck , A Hctor. The presentation, course and outcome of COVID-19 infection in people with Prader-Willi syndrome: unexpected findings from an international survey. *Orphanet J Rare Dis.* 2022 Feb 21;17(1):69.

**Abstract** Background: Prader-Willi syndrome (PWS), is a genetically determined neurodevelopmental disorder, associated with intellectual disabilities and a high incidence of obesity, diabetes mellitus, and respiratory disorders. We hypothesised that COVID-19, a viral infection which more severely affects people with these conditions, would, in people with PWS, present atypically and result in severe outcomes.

Method: A structured on-line questionnaire was piloted with parents and professionals at the International Prader-Willi Syndrome Organization (IPWSO) and promoted internationally through their global network.

Family members/other carers were asked to complete if someone they cared for with PWS was strongly suspected or confirmed as having COVID-19.

Results: Over 1 year of the pandemic 72 responses were received, 47 adults, 25 children. The following underlying conditions were present: 16 people with PWS were overweight and 18 obese, five had diabetes mellitus and 18 sleep apnoea. Main presenting symptoms were raised temperature, fatigue/daytime sleepiness, dry cough, headache/pain, and feeling unwell, with illnesses generally lasting less than a week. Length of illness was not significantly related to age, BMI, sex, or genetic subtype. No one was ventilated or in an intensive care unit or died, one person was in hospital for four days needing oxygen.

Conclusions: Contrary to our hypothesis, the PWS cohort had asymptomatic infection or mild illness. A possible explanation, supported by anecdotal evidence from parents and professional carers, is that people with PWS have a degree of innate immunity to viral infections. However, likely selection effects and a relatively low number of responses means that further evidence is needed to test this hypothesis.

Keywords: COVID-19; Innate immunity; Outcome; Prader-Willi syndrome; Symptoms.

PMID: 35189933 DOI: 10.1186/s13023-022-02228-6

Lionne N Grootjen , Nathalie E M Uyl , Inge A L P van Beijsterveldt , Layla Damen , Gerthe F Kerkhof , Anita C S Hokken-Koelega. Prenatal and Neonatal Characteristics of Children with Prader-Willi Syndrome. *J Clin Med.* 2022 Jan 28;11(3):679.

**Abstract** Objective: Prader-Willi syndrome (PWS) is a rare genetic syndrome with a wide spectrum of clinical features in early life. Late diagnoses are still present. We characterized the perinatal and neonatal features of



PWS, compared them with those of healthy newborns and assessed the prenatal and neonatal differences between the genetic subtypes.

**Design:** A cohort study in children with PWS. The prevalence of variables was compared with healthy infants (PLUTO cohort) and to population statistics from literature.

**Patients:** 244 infants with PWS and 365 healthy infants.

**Measurements:** Data on prenatal and neonatal variables in both cohorts. Population statistics were collected through an extensive literature search.

**Results:** A higher prevalence of maternal age >35 years was found in PWS compared to healthy infants and population statistics, and the highest maternal age was found in the mUPD group. Higher prevalence of polyhydramnios, caesarean section, labour induction and breech presentation, and lower birth weight SDS was found in PWS compared to healthy infants. High prevalences of decreased fetal movements (78.5%), hypotonia (100%), cryptorchism (95.9%) and poor sucking/tube feeding (93.9%) were found in PWS.

**Conclusions:** This study presents an overview of prenatal and neonatal variables in infants with PWS compared to healthy infants. Our findings may increase clinical awareness of the early perinatal signs of PWS by obstetricians, neonatologists and all those involved in infant care, enabling early diagnosis and start of multidisciplinary treatment.

**Keywords:** Prader-Willi Syndrome; children; neonate; prenatal.

PMID: 35160130 DOI: 10.3390/jcm11030679

Charlotte Höybye, Maithé Tauber. Approach to the patient with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2022 Feb 12;dgac082. Online ahead of print.

**Abstract** Prader-Willi syndrome (PWS) is a rare, multi-systemic, genetic disorder involving the hypothalamus. It is caused by loss of expression of paternally inherited genes in chromosome 15 q11-13 region. The estimated incidence is around 1 in 20.000 births. PWS is characterized by a complex lifelong trajectory involving neurodevelopmental, nutritional, endocrine, metabolic and behavioral changes. The major symptoms are hypotonia, short stature, hypogonadism, and eating disorders ranging from anorexia in infancy to hyperphagia, a deficit of satiety, and a high risk of severe obesity. The patients display intellectual disability comprising cognitive deficit, delayed motor, and language development, learning deficits, impaired social skills, and emotional regulation. Behavioral features including temper outbursts, anxiety, obsessive-compulsive symptoms and rigidity are common and become more apparent with increasing age. Almost all have hypogonadism and growth hormone deficiency. Central adrenal insufficiency is rare whereas central hypothyroidism occurs in up to 30% of children with PWS. The prevalence of obesity increases with age from almost none in early childhood to more than 90% in adulthood. Up to 25% of adults with obesity have type 2 diabetes. Obesity and its complications are the major causes of comorbidity and mortality in PWS. As there is no specific treatment care consists of comprehensive management of feeding disorders, a restricted, controlled diet, regular exercise, hormone substitution and screening and treatment of comorbidities. Here we present the course of PWS from birth to adulthood in two patients and discuss their symptoms in relation to the literature.

**Keywords:** Prader-Willi syndrome; children and adults; clinical characteristics; treatment.

PMID: 35150573 DOI: 10.1210/clinem/dgac082

Nicole Campbell, Scott Van Zant, Joyce Lammers. Multifactorial influences on successful health outcomes for an adolescent with Prader-Willi syndrome: a qualitative case study. *Physiother Theory Pract.* 2022 Jan 31;1-9. Online ahead of print.

**Abstract** Purpose: Prader-Willi syndrome (PWS) is the most common syndromic cause of childhood obesity. This qualitative case study aimed to identify and describe lifestyle themes of an adolescent with PWS that resulted in maintenance of a healthy body mass index (BMI).

**Case description:** The 16-year-old female demonstrated failure to thrive upon birth and underwent 9 months supplemented tube feeding, achieving 50<sup>th</sup> percentile weight for height. Throughout childhood she received treatment of physical, occupational, and speech therapies, and has maintained a healthy BMI ranging from 25-50<sup>th</sup> percentile weight for height.

**Methods and results:** Two video interviews were completed separately. Qualitative analysis of the transcribed data identified two overarching themes for maintaining a healthy BMI in this adolescent: 1) adolescent and parent individual characteristics; and 2) family dynamics and lifestyle. Adolescent and parental characteristics

included: high level of cognitive function for diagnosis, mild hyperphagia, desire for a regimented schedule, parental type A personalities, intentionality in parental decisions/actions. Family lifestyle characteristics included strong parental involvement and well-defined expectations for their daughter, purposeful integration of physical activity into lifestyle, and presence of a strong family support system.

Conclusion: The convergence of multiple optimal influences provided an ideal health outcome in the adolescent.

Keywords: Prader-Willi syndrome; body mass index; dietary intake; physical activity; qualitative research  
PMID: 35100943 DOI: 10.1080/09593985.2022.2036277

## Genetics and brain imaging

Tomohiro Okuda, Masaharu Moroto, Toshiyuki Yamamoto. Noninvasive prenatal testing suggesting an abnormality in chromosome 15 confirmed to be a case of Prader-Willi syndrome caused by trisomy rescue in the neonatal period. *J Obstet Gynaecol Res.* 2022 Mar 23. Online ahead of print

**Abstract** We report a case of a neonatal diagnosis of Prader-Willi syndrome caused by uniparental disomy. A 34-year-old pregnant woman underwent noninvasive prenatal testing (NIPT) in a hospital that was not certified by the Japanese Association of Medical Sciences. The results of trisomy 13, 18, and 21 were negative; however, a possible abnormality in chromosome 15 was indicated by the Z-score. Genetic counseling was not performed; thus, the woman did not understand the implication of this result. Therefore, she continued with the pregnancy and delivered a boy weighing 1892 g with hypogonadism at 38 weeks and 5 days. The infant was diagnosed with Prader-Willi syndrome caused by uniparental disomy derived from trisomy rescue. The NIPT results may have reflected placental mosaicism, emphasizing the importance of understanding the limitations of NIPT due to the presence of congenital chromosomal abnormalities that cannot be detected by NIPT platforms.

Keywords: Prader-Willi syndrome; chromosome 15; confined placental mosaicism; noninvasive prenatal testing; trisomy rescue.

PMID: 35322506 DOI: 10.1111/jog.15236

Kenichi Yamada, Masaki Watanabe, Kiyotaka Suzuki. Differential volume reductions in the subcortical, limbic, and brainstem structures associated with behavior in Prader-Willi syndrome. *Sci Rep.* 2022 Mar 23;12(1):4978.

**Abstract** Individuals with Prader-Willi syndrome (PWS) exhibit complex behavioral characteristics, including hyperphagia, autistic features, and subsequent age-related maladaptive behaviors. While this suggests functional involvements of subcortical, limbic, and brainstem areas, developmental abnormalities in such structures remain to be investigated systematically. Twenty-one Japanese individuals with PWS and 32 healthy controls with typical development were included. T<sub>1</sub>-weighted three-dimensional structural magnetic resonance images were analyzed for subcortical, limbic, and brainstem structural volumes, with age as a covariate, using a model-based automatic segmentation tool. Correlations were determined between each volume measurement and behavioral characteristics as indexed by questionnaires and block test scores for hyperphagia (HQ), autistic and obsessional traits, non-verbal intelligence (IQ), and maladaptive behavior (VABS<sub>mal</sub>). Compared with the control group, the PWS group showed significantly reduced relative volume ratios per total intracranial volume (TIV) in thalamus, amygdala, and brainstem structures, along with TIV and native volumes in all substructures. While the brainstem volume ratio was significantly lower in all age ranges, amygdala volume ratios were significantly lower during early adulthood and negatively correlated to HQ and VABS<sub>mal</sub> but positively correlated to Kohs IQ. Thus, limbic and brainstem volume alterations and differential volume trajectories may contribute to the developmental and behavioral pathophysiology of PWS.

PMID: 35322075 DOI: 10.1038/s41598-022-08898-3

Guanghan Jia , Yazhou Cui , Liang Shi , Jing Luan , Jing Wang , Jingxiang Han. Generation of a transgene-free induced pluripotent stem cell line (SMBCi011-A) from a patient with Prader-Willi syndrome. *Stem Cell Res.* 2022 Feb 12;60:102695. Online ahead of print.

**Abstract** Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by deficiency of paternal gene expression in the 15q11.2-q13 chromosome imprinted region. Hyperphagia and dysgnosia are typical clinical features in the early-childhood of patient. We generated an induced pluripotent stem cell (iPSC) line SMBCi011-A from a 6 years old male PWS patient, the line expressed pluripotent signs and had ability to differentiate into three germ layers in vivo.

PMID: 35203049 DOI: 10.1016/j.scr.2022.102695

Jiadi Wen , Hongyan Chai , Brittany Grommisch , Autumn DiAdamo , Daniel Dykas , Deqiong Ma , Andreea Popa , Chen Zhao , Michele Spencer-Manzon , Yong-Hui Jiang , James McGrath , Peining Li , Allen Bale , Hui Zhang. Detecting regions of homozygosity improves the diagnosis of pathogenic variants and uniparental disomy in pediatric patients. *Am J Med Genet A.* 2022 Feb 23. Online ahead of print.

**Abstract** Chromosomal microarray analysis using single nucleotide polymorphism probes can detect regions of homozygosity (ROH). This confers a potential utility in revealing autosomal recessive (AR) diseases and uniparental disomy (UPD). Results of genetic testing among pediatric patients from 2015 to 2019 were evaluated. Diagnostic findings with detected ROH from large consecutive case series in the literature were reviewed. Of 2050 pediatric patients, 65 (3%) had one or more ROH and 31 (53%) had follow-up whole exome sequencing (WES) and methylation studies. Seven homozygous variants were detected and four of them from three patients (9.6%) were within the detected ROH and classified as pathogenic or likely pathogenic variants for AR diseases. One patient (3%) had segmental UPD15q for a diagnosis of Prader-Willi syndrome. Additive diagnostic yield from ROH reporting was at least 0.2% (4/2050) of pediatric patients. These results were consistent with findings from several large case series reported in the literature. Detecting ROH had an estimated baseline predictive value of 10% for AR diseases and 3% for UPD. Consanguinity revealed by multiple ROH was a strong predictor for AR diseases. These results provide evidence for genetic counseling and recommendation of follow-up WES and methylation studies for pediatric patients reported with ROH.

Keywords: array comparative genomic hybridization (aCGH); autosomal recessive (AR) disease; pathogenic variant; regions of homozygosity (ROH); uniparental disomy (UPD); whole exome sequencing (WES).

PMID: 35199448 DOI: 10.1002/ajmg.a.62693

Kana Marunaka , Shokoku Shu , Mao Kobayashi , Makiko Goto , Yuji Katsuta , Yuta Yoshino , Akira Ikari. Elevation of Hyaluronan Synthase by Magnesium Supplementation Mediated through the Activation of GSK3 and CREB in Human Keratinocyte-Derived HaCaT Cells. *Int J Mol Sci.* 2021 Dec 22;23(1):71.

**Abstract** Skin barrier damage is present in the patients with hereditary disorders of the magnesium channel, but the molecular mechanism has not been fully understood. We found that the expressions of hyaluronan synthase (HAS), HAS2 and HAS3 are influenced by MgCl<sub>2</sub> concentration in human keratinocyte-derived HaCaT cells. The exposure of cells to a high concentration (5.8 mM) of MgCl<sub>2</sub> induced the elevation of HAS2/3 expression, which was inhibited by mRNA knockdown of nonimprinted in Prader-Willi/Angelman syndrome-like domain containing 4 (NIPAL4). Similarly, the content of hyaluronic acid (HA) was changed according to MgCl<sub>2</sub> concentration and the expression of NIPAL4. The MgCl<sub>2</sub> supplementation increased the reporter activities of HAS2/3, which were inhibited by NIPAL4 knockdown, indicating that the expressions of HAS2/3 are up-regulated at the transcriptional level. The reporter activities and mRNA levels of HAS2/3, and the production of HA were inhibited by CHIR-99021, a glycogen synthase kinase-3 (GSK3) inhibitor, and naphthol AS-E, a cyclic AMP-response element binding protein (CREB) inhibitor. Furthermore, the mutation in putative CREB-binding sites of promoter region in HAS2/3 genes inhibited the MgCl<sub>2</sub> supplementation-induced elevation of promoter activity. Our results indicate that the expressions of HAS2/3 are up-regulated by MgCl<sub>2</sub> supplementation in HaCaT cells mediated through the activation of GSK3 and CREB. Magnesium may play a pivotal role in maintaining the skin barrier function and magnesium supplementation may be useful to enhance moisturization and wound repair in the skin.

Keywords: hyaluronan synthase; hyaluronic acid; magnesium

PMID: 35008494 DOI: 10.3390/ijms23010071

Kenichi Yamada 1, Junichi Yoshimura 2, Masaki Watanabe 1, Kiyotaka Suzuki 1. Application of 7 tesla magnetic resonance imaging for pediatric neurological disorders: Early clinical experience. *J Clin Imaging Sci.* 2021 Dec 2;11:65. eCollection 2021

**Abstract** Ultra-high field magnetic resonance imaging (MRI) has been introduced for use in pediatric developmental neurology. While higher magnetic fields have certain advantages, optimized techniques with specific considerations are required to ensure rational and safe use in children and those with pediatric neurological disorders (PNDs). Here, we summarize our initial experience with clinical translational studies that utilized 7 tesla (T)-MRI in the fields of developmental neurology. T2-reversed images and three-dimensional anisotropy contrast imaging enabled the depiction of targeted pathological brain structures with better spatial resolution. Diffusion imaging and susceptibility-weighted imaging enabled visualization of intracortical, subcortical, and intratumoral microstructures *in vivo* within highly limited scan times appropriate for patients with PNDs. 7T-MRI appears to have significant potential to enhance the depiction of the structural and functional properties of the brain, particularly those associated with atypical brain development.

**Keywords:** 7 Tesla; Brain development; Brain tumor; Prader–Willi syndrome; Three-dimensional anisotropy contrast.

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David E Godler , Ling Ling , Dinusha Gamage , Emma K Baker , Minh Bui , Michael J Field , Carolyn Rogers , Merlin G Butler , Alessandra Murgia , Emanuela Leonardi , Roberta Polli , Charles E Schwartz , Cindy D Skinner , Angelica M Allende , Lorena Santa Maria , James Pitt , Ronda Greaves , David Francis , Ralph Oertel , Min Wang , Cas Simons , David J Amor. Feasibility of Screening for Chromosome 15 Imprinting Disorders in 16 579 Newborns by Using a Novel Genomic Workflow. *JAMA Netw Open* . 2022 Jan 4;5(1):e2141911

**Abstract** Importance: Newborn screening for Angelman syndrome (AS), Prader-Willi syndrome (PWS), and chromosome 15 duplication syndrome (Dup15q) may lead to benefit from early diagnosis and treatment. Objective: To examine the feasibility of newborn screening for these chromosome 15 imprinting disorders at population scale.

**Design, setting, and participants:** In this diagnostic study, the validation data set for the first-tier SNRPN test, called methylation-specific quantitative melt analysis (MS-QMA), included 109 PWS, 48 AS, 9 Dup15q, and 1190 population control newborn blood spots (NBS) and peripheral tissue samples from participants recruited from January 2000 to December 2016. The test data set included NBS samples from 16 579 infants born in 2011. Infants with an NBS identified as positive for PWS, AS, or Dup15q by the first-tier test were referred for droplet digital polymerase chain reaction, real-time polymerase chain reaction, and low-coverage whole-genome sequencing for confirmatory testing. Data analyses were conducted between February 12, 2015, and August 15, 2020.

**Results:** In the validation data set, the median age for the 77 patients with PWS was 3.00 years (IQR, 0.01-44.50 years); for the 46 patients with AS, 2.76 years (IQR, 0.028 to 49.00 years); and for the 9 patients with Dup15q, 4.00 years (IQR, 1.00 to 28.00 years). Thirty-eight patients (51.4%) in the PWS group, 20 patients (45.5%) in the AS group, and 6 patients (66.7%) in the Dup15q group who had sex reported were male. The validation data set showed MS-QMA sensitivity of 99.0% for PWS, 93.8% for AS, and 77.8% for Dup15q; specificity of 100% for PWS, AS, and Dup15q; positive predictive and negative predictive values of 100% for PWS and AS; and a positive predictive value of 87.5% and negative predictive value of 100% for Dup15q. In the test data set of NBS samples from 16 579 infants, 92 had a positive test result using a methylation ratio cut-off of 3 standard deviations from the mean. Of these patients, 2 were confirmed to have PWS; 2, AS; and 1, maternal Dup15q. With the use of more conservative PWS- and AS-specific thresholds for positive calls from the validation data set, 9 positive NBS results were identified by MS-QMA in this cohort. The 2 PWS and 2 AS calls were confirmed by second-tier testing, but the 1 Dup15q case was not confirmed. Together, these results provided prevalence estimates of 1 in 8290 for both AS and PWS and 1 in 16 579 for maternal Dup15q, with positive predictive values for first-tier testing at 67.0% for AS, 33.0% for PWS, and 44.0% for combined detection of chromosome 15 imprinting disorders for the validation data set.

**Conclusions and relevance:** The findings of this diagnostic study suggest that it is feasible to screen for all chromosome 15 imprinting disorders using SNRPN methylation analysis, with 5 individuals identified with these disorders out of 16 579 infants screened

## Endocrine including GH

Aitana Ayet-Roger, Lorena Joga-Elvira, Assumpta Caixàs, Raquel Corripio. Cognitive and Adaptive Effects of Early Growth Hormone Treatment in Prader-Willi Syndrome Patients: A Cohort Study. *J Clin Med.* 2022 Mar 14;11(6):1592.

**Abstract** Background: Prader-Willi Syndrome (PWS) is a genetically based neurodevelopmental disease characterized by obesity, hyperphagia, and mild to moderate intellectual disability. Treatment with growth hormone (GH) could provide cognitive benefits. The objective of the present study was to compare the cognitive and adaptive performance of 31 patients with genetically confirmed PWS grouped in two cohorts, one treated with GH before 2 years old (Group 1) and the other receiving the treatment later (Group 2).

Method: We compared two variables necessary to diagnose intellectual disability: intellectual performance, using the Weschler scales, and adaptive behavior, using the DABS scale. The scores were analyzed by means of non-parametric statistical tests.

Results: Group 1 ( $n = 10$ ) obtained higher and statistically significant scores in Total Intelligence Quotient (TIQ), General Ability Index (GAI), and General Adaptive Behavior (GAB), implying better cognitive and adaptive performance compared to Group 2.

Conclusions: Treatment with GH should be administered in the early stage of development (before 2 years old) to obtain greater benefits at the cognitive and adaptive levels.

Keywords: Prader-Willi Syndrome; adaptive behavior; cognition; growth hormone treatment.

PMID: 35329918 PMCID: PMC8955812 DOI: 10.3390/jcm11061592

Marta Drabik, Andrzej Lewiński, Renata Stawerska. Management of Prader-Labhart-Willi syndrome in children and in adults, with particular emphasis on the treatment with recombinant human growth hormone. *Pediatr Endocrinol Diabetes Metab.* 2022;28(1):64-74.

**Abstract** Introduction: Prader-Willi syndrome (PWS) is a genetically determined disease that manifests itself in a number of abnormalities resulting, among others, from dysfunction of the hypothalamic-pituitary system. Only integrated, multidisciplinary care gives patients the chance to significantly improve the quality of life and achieve a life expectancy that does not differ from the general population.

Aim: The aim of the study was to summarize the available literature on the management of patients suffering from PWS.

Conclusions: More and more reports based on clinical trials conducted around the world indicate the undeniable benefits of rhGH therapy in patients with PWS in childhood and after the end of growth period. They consist in improving the body composition, improving the lipid profile, increasing bone mineral density and improving the mental state and patients' quality of life.

Keywords: metabolism; obesity; recombinant human growth hormone; therapeutic program.; Prader-Willi syndrome.

PMID: 35307998 DOI: 10.5114/pedm.2022.112861

Masanobu Kawai, Yuri Etani, Shinobu Ida. Subcutaneous adipose tissue is a positive predictor for bone mineral density in prepubertal children with Prader-Willi syndrome independent of lean mass. *J Pediatr Endocrinol Metab.* 2022 Mar 15. Online ahead of print.

**Abstract** Objectives: Emerging evidence suggests a fat depot-specific relationship with bone mineral density (BMD) in children, particularly in those who are overweight/obese. However, this has not yet been investigated in detail in children with Prader-Willi syndrome (PWS), a genetic syndrome characterized by a decreased lean mass (LM) and increased fat mass (FM). The objective of this study is to investigate the relationships of LM and FM, particularly fat distribution, with bone mineral parameters.

**Methods:** This is a retrospective and cross-sectional study. Forty-seven prepubertal Japanese children with PWS (22 males, mean age: 6.86 years) were included. No subjects had type 2 diabetes mellitus or osteoporotic medications. LM, FM, and BMD and bone mineral content in the total body less head and the lumbar spine were measured using dual-energy x-ray absorptiometry, in addition to subcutaneous/visceral adipose tissue (SAT/VAT), and the ratio of VAT to SAT (V/S) by computed tomography at the umbilical level. Bone mineral apparent density was calculated to correct for bone size.

**Results:** LM positively correlated with bone mineral parameters after controlling for age, sex, growth hormone (GH) treatment, and FM. Although FM did not correlate with bone mineral parameters, compartment-specific analysis revealed that SAT positively and V/S negatively correlated with bone mineral parameters after controlling for age, sex, GH treatment and LM.

**Conclusions:** A compartment-specific effect of FM on bone mineral parameters was noted such that SAT was a positive predictor for BMD independent of LM in prepubertal children with PWS.

**Keywords:** Prader–Willi syndrome; adiposity; bone mineral density; children; fat distribution.

PMID: 35286052 DOI: 10.1515/jpem-2021-0749

Maria Rosaria Licenziati , Dario Bacchini , Antonino Crinò , Graziano Grugni , Danilo Fintini , Sara Osimani , Letizia Ragusa , Michele Sacco , Lorenzo Iughetti , Luisa De Sanctis , Adriana Franzese , Malgorzata Gabriela Wasniewska , Maria Felicia Faienza , Maurizio Delvecchio , Concetta Esposito , Giuliana Valerio. The Hyperphagia Questionnaire: Insights From a Multicentric Validation Study in Individuals With Prader Willi Syndrome. *Front Pediatr.* 2022 Feb 14;10:829486. eCollection 2022.

**Abstract** Background/objectives: The present study aimed to validate the Italian version of the Hyperphagia Questionnaire (HQ), a 11-items questionnaire developed to assess hyperphagia in individuals with Prader-Willi syndrome (PWS). This is a complex neurodevelopmental disorder characterized by endocrine dysfunction, hypotonia, intellectual disability, psychiatric disorders and obesity.

**Methods:** Parents of 219 individuals with PWS (age range 3-54 years;  $M_{age} = 17.90$ ; 108 Males), recruited in 12 hospitals in Italy responded to HQ during routine visits. In function of the level of analyses the sample was divided into two subgroups (<18> years) or into four age-subgroups (2.5-4.5; 4.5-8; 8-18; >18 years) corresponding to different clinical stages.

**Results:** Confirmatory factor analysis (CFA) confirmed the three hyperphagic subdimensions of the original structure (behavior, drive, and severity), but one item was dropped out, reducing the final version to 10 items. Using multi-group CFA, HQ showed satisfactory indexes of measurement invariance by age. Good indexes of internal consistency (Cronbach's alpha and McDonald's Omega coefficients) were found for each subdimension. The three hyperphagia subdimensions positively converged with other food-related measures: emotional overeating, food enjoyment, food responsiveness, and satiety responsiveness. A significant increase of all hyperphagic subdimensions was found across age groups. Higher hyperphagic levels were found in participants with higher body mass index. Hyperphagic drive differently increased in function of the interaction between age and underlying genetic mechanisms.

**Conclusion:** The Italian version of the HQ is a psychometrically valid and reliable instrument for assessing hyperphagia in individuals with PWS. This tool may prove useful to evaluate the efficacy of pharmacologic and rehabilitative treatments.

**Keywords:** Genetic Obesity; Prader-Willi syndrome; assessment; hyperphagia; multicentric study; weight status.

PMID: 35237541 PMID: PMC8884358 DOI: 10.3389/fped.2022.829486

Assumpta Caixàs. Prader-Willi syndrome: Making progress, one step at a time *Endocrinol Diabetes Nutr (Engl Ed).* 2022 Jan;69(1):1-3. Epub 2022 Feb 8.

PMID: 35232554 DOI: 10.1016/j.endien.2022.01.003

Brittney Knott , Matthew A Kocher , Henry A Paz , Shelby E Hamm , William Fink , Jordan Mason , Robert W Grange , Umesh D Wankhade , Deborah J Good. Dietary Conjugated Linoleic Acid Reduces Body Weight and Fat in *Snord116<sup>m+/p-</sup>* and *Snord116<sup>m-/p-</sup>* Mouse Models of Prader-Willi Syndrome. *Nutrients* 2022 Feb 18;14(4):860.

**Abstract** Prader-Willi Syndrome (PWS) is a human genetic condition that affects up to 1 in 10,000 live births. Affected infants present with hypotonia and developmental delay. Hyperphagia and increasing body weight follow unless drastic calorie restriction is initiated. Recently, our laboratory showed that one of the genes in the deleted locus causative for PWS, *Snord116*, maintains increased expression of hypothalamic *Nhlh2*, a basic helix-loop-helix transcription factor. We have previously also shown that obese mice with a deletion of *Nhlh2* respond to a conjugated linoleic acid (CLA) diet with weight and fat loss. In this study, we investigated whether mice with a paternal deletion of *Snord116* (*Snord116*<sup>m+/p-</sup>) would respond similarly. We found that while *Snord116*<sup>m+/p-</sup> mice and mice with a deletion of both *Snord116* alleles were not significantly obese on a high-fat diet, they did lose body weight and fat on a high-fat/CLA diet, suggesting that the genotype did not interfere with CLA actions. There were no changes in food intake or metabolic rate, and only moderate differences in exercise performance. RNA-seq and microbiome analyses identified hypothalamic mRNAs, and differentially populated gut bacteria, that support future mechanistic analyses. CLA may be useful as a food additive to reduce obesity in humans with PWS.

Keywords: RNA-seq; Snord116; dietary intervention; exercise; microbiome; muscle function; obesity.

PMID: 35215509 DOI: 10.3390/nu14040860

Jennifer L Miller, André Lacroix, Lynne M Bird, Ashley H Shoemaker, Andrea Haqq, Cheri L Deal, Kristie A Clark, Michael H Ames, Jeffrey G Suico, Amparo de la Peña, Caroline Fortier. The Efficacy, Safety, and Pharmacology of a Ghrelin O-Acyltransferase Inhibitor for the Treatment of Prader-Willi Syndrome. *J Clin Endocrinol Metab.* 2022 Feb 25;dgac105. Online ahead of print.

**Abstract** Context: Acylated ghrelin (AG) stimulates appetite and is elevated compared to its unacylated (UAG) counterpart in Prader-Willi syndrome (PWS). GLWL-01 is a selective, reversible inhibitor of ghrelin-O-acyltransferase (GOAT), the enzyme that converts UAG into AG.

Objective: Assess the efficacy, pharmacokinetics, pharmacodynamics, and safety of GLWL-01 in the treatment of PWS patients.

Design: Double-blind, placebo-controlled Phase 2 crossover study with two active treatment periods of 28-days in 19 patients (16 to 65 years; body mass index (BMI)  $\geq 28$  kg/m<sup>2</sup>) with genetically confirmed PWS.

Setting: Seven hospital-based study centers in the US and Canada.

Intervention: Patients received placebo or GLWL-01 (450 mg twice daily) orally after lead-in placebo and washout periods.

Main outcome: The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) and Caregiver Global Impression of Change (CGIC) were used to measure reductions in hyperphagia. Plasma concentrations of AG and UAG were evaluated as correlates.

Results: Treatment resulted in significant differences compared to placebo in plasma AG ( $p=0.0002$ ), UAG ( $p=0.0488$ ), and AG/UAG ( $p=0.0003$ ). GLWL-01 did not significantly reduce hyperphagia-related behavior or bring about changes in global clinical endpoints, as assessed by caregivers. Anthropometric and clinical parameters correlated with obesity did not significantly change in response to treatment. Less than half of patients reported a treatment emergent adverse event (TEAE). No deaths, serious adverse events, or severe TEAEs were reported.

Conclusions: GLWL-01 was safe and well-tolerated. Pharmacological parameters confirmed the inhibition of GOAT following administration of GLWL-01. Patients' eating behaviors, BMI, blood glucose, and total cholesterol, among other similar measures, were not modified.

Keywords: GLWL-01; Prader-Willi Syndrome (PWS); acylated ghrelin (AG); ghrelin; ghrelin o-acyltransferase (GOAT).

PMID: 35213714 DOI: 10.1210/clinem/dgac105

Massimiliano Orso, Barbara Polistena, Simona Granato, Giuseppe Novelli, Roberto Di Virgilio, Daria La Torre, Daniela d'Angela, Federico Spandonaro. Pediatric growth hormone treatment in Italy: A systematic review of epidemiology, quality of life, treatment adherence, and economic impact. *PLoS One.* 2022 Feb 25;17(2):e0264403.eCollection 2022.

**Abstract** Objectives: This systematic review aims to describe 1) the epidemiology of the diseases indicated for treatment with growth hormone (GH) in Italy; 2) the adherence to the GH treatment in Italy and factors

associated with non-adherence; 3) the economic impact of GH treatment in Italy; 4) the quality of life of patients treated with GH and their caregivers in Italy.

**Methods:** Systematic literature searches were performed in PubMed, Embase and Web of Science from January 2010 to March 2021. Literature selection process, data extraction and quality assessment were performed by two independent reviewers. Study protocol has been registered in PROSPERO (CRD42021240455).

**Results:** We included 25 studies in the qualitative synthesis. The estimated prevalence of growth hormone deficiency (GHD) was 1/4,000-10,000 in the general population of children; the prevalence of Short Stature Homeobox Containing gene deficiency (SHOX-D) was 1/1,000-2,000 in the general population of children; the birth prevalence of Turner syndrome was 1/2,500; the birth prevalence of Prader-Willi syndrome (PWS) was 1/15,000. Treatment adherence was suboptimal, with a range of non-adherent patients of 10-30%. The main reasons for suboptimal adherence were forgetfulness, being away from home, pain/discomfort caused by the injection. Economic studies reported a total cost for a complete multi-year course of GH treatment of almost 100,000 euros. A study showed that drug wastage can amount up to 15% of consumption, and that in some Italian regions there could be a considerable over- or under-prescribing. In general, patients and caregivers considered the GH treatment acceptable. There was a general satisfaction among patients with regard to social and school life and GH treatment outcomes, while there was a certain level of intolerance to GH treatment among adolescents. Studies on PWS patients and their caregivers showed a lower quality of life compared to the general population, and that social stigma persists.

**Conclusion:** Growth failure conditions with approved GH treatment in Italy constitute a significant burden of disease in clinical, social, and economic terms. GH treatment is generally considered acceptable by patients and caregivers. The total cost of the GH treatment is considerable; there are margins for improving efficiency, by increasing adherence, reducing drug wastage and promoting prescriptive appropriateness.

PMID: 35213607 PMCID: PMC8880399 DOI: 10.1371/journal.pone.0264403

D Turkkahraman, E C Sirazi, G Aykal. Serum alpha-melanocyte-stimulating hormone (a-MSH), brain-derived neurotrophic factor (BDNF), and agouti-related protein (AGRP) levels in children with Prader-Willi or Bardet-Biedl syndromes. *J Endocrinol Invest.* 2022 Jan 31. Online ahead of print.

**Abstract** Background: Although leptin/melanocortin pathway pathologies in hypothalamus are thought to be the main cause of early-onset obesity and hyperphagia in PWS and BBS, the exact mechanism is still not known.

**Objective:** To measure serum concentrations of a-MSH, BDNF and AGRP in a group of children with BBS or PWS.

**Methods:** We recruited 12 subjects with PWS, 12 subjects with BBS, 28 obese controls (OC) and 26 lean controls (LC) matched for age, sex and puberty. Serum a-MSH, BDNF and AGRP levels were measured by the ELISA method.

**Results:** The mean a-MSH level was lower in PWS than those of OC and LC ( $3729 \pm 1319$ ,  $5211 \pm 829$  and  $5681 \pm 565$  pg/ml, respectively,  $p < 0.001$ ), and mean a-MSH was lower in OC than LC ( $p < 0.05$ ). The mean BDNF level of PWS was higher than those of OC and LC ( $565 \pm 122$ ,  $482 \pm 102$  and  $391 \pm 74$  pg/ml, respectively,  $p < 0.001$ ). On the other hand, mean a-MSH level of BBS was lower than those of OC and LC ( $4543 \pm 658$ ,  $5211 \pm 829$  and  $5681 \pm 565$  pg/ml, respectively,  $p < 0.001$ ), and mean a-MSH was lower in OC than LC ( $p < 0.05$ ). The mean BDNF level of BBS was higher than those of OC and LC ( $583 \pm 115$ ,  $482 \pm 102$  and  $391 \pm 74$  pg/ml, respectively,  $p < 0.001$ ). Additionally, both in PWS and BBS, the mean BDNF level was higher in OC than LC ( $p < 0.01$ ). Regarding AGRP level, there was no difference both in BBS and PWS compared to OC.

**Conclusion:** We found that the serum a-MSH levels of PWS and BBS groups are significantly lower compared to those of obese and lean controls. Therefore, we can speculate that the circulating a-MSH level does properly reflect its central production, and the serum a-MSH level might be a good biomarker to detect a-MSH deficiency in individuals suspected to have BBS or PWS, and also in those with POMC, PCSK1, and LEPR deficiency.

**Keywords:** AGRP; BBS; BDNF; PWS; a-MSH.

PMID: 35098494 DOI: 10.1007/s40618-021-01737-8



Isabella Albanese , Natasha Garfield. A Case Report of Hyperestrogenism in Prader-Willi Syndrome. *AACE Clin Case Rep.* 2021 Jun 12;8(1):6-7. eCollection Jan-Feb 2022.

**Abstract** Objective: Prader-Willi syndrome (PWS) is associated with multiple endocrinopathies, including hypogonadism. The mechanism underlying hypogonadism in PWS is thought to be secondary to hypothalamic dysfunction, primary gonadal defect, or a combination of both. Here, we present a case of hyperestrogenism in PWS due to concomitant polycystic ovary syndrome (PCOS) and therapeutic considerations regarding hormone replacement therapy (HRT).

Case report: An 18-year-old woman with PWS transferred to adult care from pediatrics was found to have hyperestrogenism (specifically, elevated estrone with normal estradiol levels). Additionally, she demonstrated oligomenorrhea and hyperandrogenism, meeting diagnostic criteria for PCOS. After 3 months of therapy with cyclic medroxyprogesterone alone, she developed normal withdrawal bleeding.

Discussion: Given the elevated estrone and normal estradiol levels, our patient's hyperestrogenism is thought to be a direct result of her hyperandrogenism due to peripheral conversion. Prolonged exposure to unopposed estrogen is an established risk factor for endometrial cancer development in PCOS; thus, this was taken into account regarding her HRT, and she was treated with cyclic progesterone alone.

Conclusion: Women with PWS are typically treated with combined estrogen and progesterone HRT; however, our case, a unique presentation of PCOS in PWS, demonstrated the importance of tailoring HRT to a patient's specific needs.

Keywords: FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; LH, luteinizing hormone; PCOS; PCOS, polycystic ovary syndrome; PWS, Prader-Willi syndrome; Prader-Willi syndrome; estrogen; testosterone.

PMID: 35097192 PMID: PMC8784723 DOI: 10.1016/j.aace.2021.06.003

Su Jin Kim , Sung Yoon Cho , Dong-Kyu Jin. Prader-Willi syndrome: an update on obesity and endocrine problems. *Ann Pediatr Endocrinol Metab* 2021 Dec;26(4):227-236. Epub 2021 Dec 31.

**Abstract** Prader-Willi syndrome (PWS) is a rare complex genetic disorder that results from a lack of expression of the paternally inherited chromosome 15q11-q13. PWS is characterized by hypotonia and feeding difficulty in early infancy and development of morbid obesity aggravated by uncontrolled hyperphagia after childhood and adolescent. Dysmorphic facial features, delayed motor and language development, various degrees of cognitive impairment, and behavioral problems are common in PWS. Without early, intensive nutritional therapy along with behavioral modification, PWS patients develop severe obesity associated with type 2 diabetes, obstructive sleep apnea, right-side heart failure, and other obesity-related metabolic complications. Hypothalamic dysfunction in PWS can lead to several endocrine disorders, including short stature with growth hormone deficiency, hypothyroidism, central adrenal insufficiency, and hypogonadism. In this review, we discuss the natural history of PWS and the mechanisms of hyperphagia and obesity. We also provide an update on obesity treatments and recommendations for screening and monitoring of various endocrine problems that can occur in PWS.

Keywords: Prader-Willi syndrome; endocrine system disease; hypothalamic dysfunction; obesity.

PMID: 34991300 DOI: 10.6065/apem.2142164.082

## Sensory and physical

Antonino Crinò , Michela Armando , Marco Crostelli , Osvaldo Mazza , Dario Bruzzese , Alessio Convertino , Danilo Fintini , Sarah Bocchini , Sara Ciccone , Alessandro Sartorio , Graziano Grugni. High Prevalence of Scoliosis in a Large Cohort of Patients with Prader-Willi Syndrome. *J Clin Med.* 2022 Mar 13;11(6):1574.

**Abstract** The characteristics of scoliosis were investigated in a large cohort of children and adults with Prader-Willi syndrome (PWS), analysing the role of age, gender, puberty, body mass index (BMI), genotype and growth hormone therapy (GHT) on its onset and severity. A retrospective cross-sectional study was performed in 180 patients with genetically confirmed PWS (96 females), aged  $17.6 \pm 12$  years. Eighty-five subjects (47%) were obese. One hundred and fifty subjects (83.3%) were on GHT, while 30 patients had never been treated. Overall, 150 subjects (83.3%) were affected by scoliosis, 80.2% of children and adolescents and 87.8% of adults. A mild degree of scoliosis was observed in 58 patients (38.7%), moderate in 43 (28.7%) and severe in 49 (32.6%). Median age at diagnosis of scoliosis was 6.3 years, while the severe forms were diagnosed earlier (median age: 3.8 years). The cumulative probability at 5 years of age was equal to 0.403 and almost doubled at 15 years. No significant associations were found between scoliosis and genotype, gender, pubertal stage, GHT and BMI. A corset was prescribed to 75 subjects (50%) at a median age of 7.5 years, while 26 subjects (17.3%) underwent surgery at a median age of 13.1 years. Our data indicate that scoliosis is one of the major concerns for PWS patients that increases with age, and therefore suggest the need for regular systematic monitoring of spinal deformity from paediatric age.

**Keywords:** Prader-Willi syndrome; growth hormone therapy; obesity; scoliosis.

PMID: 35329900 PMCID: PMC8953215 DOI: 10.3390/jcm11061574

Jun Wang , Xiushu Shen , Hong Yang , Wei Shi , Xiaoyun Zhu , Herong Gao , Huanhuan Yin , Fanzhe Meng , Yun Wu. Inter- and intra-observer reliability of the "Assessment of Motor Repertoire- 3 to 5 Months" based on video recordings of infants with Prader-Willi syndrome *BMC Pediatr.* 2022 Mar 22;22(1):150.

**Abstract** Background: The "Assessment of Motor Repertoire-3 to 5 Months", which is a part of Prechtl's General Movements Assessment (GMA), has been gradually applied to infants with genetic metabolic disorders. However, there have been no studies on the application of the GMA for infants with Prader-Willi syndrome (PWS).

**Aims:** The purpose of this study was to determine the inter- and intra-observer reliability of the assessment tool in a population of infants with PWS.

**Study design:** This was a reliability and agreement study.

**Subjects:** This was a cross-sectional study with 15 infants with PWS born at an average gestational age of 38 weeks.

**Outcome measures:** Standardized video recordings of 15 infants with PWS (corrected ages of 3 to 5 months) were independently assessed by three observers. Kappa and ICC statistics were applied in inter- and intra- observer reliability analyses.

**Results:** The overall reliability ICC values of the "Motor Optimality Score" (MOS) ranged from 0.84 to 0.98, and the pairwise agreement ranged between 0.86 and 0.95 for inter- observe reliability. In addition, ICC values for the MOS ranged between 0.95 and 0.98 for tester agreement in intra-observer reliability. Complete agreement reliability (100%) was achieved in the subcategories of "Fidgety Movements" and "Movement Character" for the inter- and intra-observer reliability. Moderate to high inter- and intra-observer reliability were found in the subcategories of "Repertoire of Co-Existent Other Movements", "Quality of Other Movements" and "Posture", with kappa values ranging between 0.63 and 1.00.

**Conclusion:** There were high levels of inter-and intra-observer agreement in the "Assessment of Motor Repertoire-3 to 5 Months" for infants with PWS. It is possible to carry out standardized quantitative assessments of the motor performance of infants with PWS.

**Keywords:** General movements assessment; Infants; Inter- and intra-observer reliability; Prader-willi syndrome.

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Songhao Hu , Biao Huang , Ken Loi , Xiaomei Chen , Qinyu Ding, Lan Luo , Cunchuan Wang, Wah Yang , Chinese Obesity and Metabolic Surgery Collaborative. Patients with Prader-Willi Syndrome (PWS) Underwent Bariatric Surgery Benefit more from High-Intensity Home Care. *Obes Surg.* 2022 Mar 15. Online ahead of print.

**Abstract** Background: Long-term weight loss effect of bariatric surgeries for patients with Prader-Willi Syndrome (PWS) remains controversial since factors like postoperative home care intensity may impact the outcome. The aim of this study was to evaluate the role of home care intensity on long-term weight loss effect of bariatric surgery in patients with PWS.

Methods: This was a prospective observational study on patients with PWS undergoing bariatric surgery and patients were enrolled from July 2015 to December 2016. Detailed information of patients' weight and behaviors was recorded by caregivers postoperatively. The intensities of home care applied to patients were classified into four categories (high, moderate, low, and very low) according to the records. Results: Six cases (3 males, 3 females) were enrolled in this study with LSG (n = 2), RYGB (n = 3), and LSG-DJB (n = 1) as their primary operation. The mean BMI of these participants was  $46.78 \pm 11.63$  kg/m<sup>2</sup>, and the mean age was  $17.66 \pm 6.59$  years. All patients had at least 5 years of follow-ups, and the %EWL were  $51.57 \pm 23.36\%$ ,  $64.54 \pm 18.97\%$ ,  $35.34 \pm 36.53\%$ ,  $19.45 \pm 41.78\%$ , and  $-4.74 \pm 71.50\%$  in the half, first, second, third, and fifth year after surgery respectively. Two patients with high-intensity home care achieved a %EWL of  $70.57 \pm 8.86\%$  in the fifth year after surgery.

Conclusions: Overall long-term weight loss of bariatric surgery for patients with PWS was not found through the follow-ups. Two patients with high-intensity home care maintained weight loss at the fifth-year follow-up, suggesting a pivotal role of high-intensity home care in long-term outcomes of bariatric surgery in patients with PWS.

Keywords: Bariatric surgery; Home care intensity; Obesity; Prader-Willi syndrome.

PMID: 35288862 DOI: 10.1007/s11695-022-05999-w

Gisela Vasconcelos , Jo S Stenehjem , Stefan Axelsson , Ronnaug Saeves. Craniofacial and dentoalveolar morphology in individuals with Prader-Willi syndrome: a case-control study. *Orphanet J Rare Dis.* 2022 Feb 22;17(1):77.

**Abstract** Background: Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder with distinct genetic and clinical features. Among other clinical symptoms, PWS is characterized by severe infantile hypotonia with feeding problems, childhood onset hyperphagia, obesity, scoliosis, short stature combined with growth hormone deficiency and developmental delay. PWS is associated with facial dysmorphology, orofacial dysfunction, oral abnormalities, low salivary flow and subsequent severe tooth wear. Little is known about the craniofacial growth direction or dental and skeletal relationships in individuals with PWS in different ages. The purpose of this study was to assess the craniofacial and dentoalveolar characteristics and to investigate the craniofacial growth direction separately in children, young adults and adults with PWS, using a cephalometric analysis of lateral cephalograms.

Results: Lateral cephalograms of 42 individuals with a confirmed genetic diagnosis of PWS were analysed and divided into three groups according to their age: Children (< 12 years), young adults (12-20 years) and adults (> 20 years). Cephalometric variables were compared between PWS patients and controls by age and sex. Significant deviations and distinct craniofacial patterns were found in children, young adults and adults with PWS compared with the control group. Children showed retrognathic mandible with a skeletal class II relationship, posterior growth direction and longer anterior face height. The young adults had smaller cranial base angle, a skeletal class II pattern and a higher anterior lower face than the control group. Adults with PWS had a prognathic mandible, skeletal class III relationship with anterior growth direction, more retroclined lower incisors and proclined upper incisors than the controls. Similar results were found when comparing the three groups with PWS; the adults had a prognathic mandible, skeletal class III pattern and anterior growth direction. Children had a repositioned mandibula, skeletal class II relationship and posterior growth direction.

Conclusion: This study may contribute to a better understanding of the craniofacial growth pattern in children, young adults and adults with PWS and may have a clinical importance when planning dental treatment, such as prosthodontics and/or orthodontics.

Keywords: Cephalometric analysis; Craniofacial; Dentoalveolar; Prader-Willi.

PMID: 35193626 DOI: 10.1186/s13023-022-02222-y

Merlin Butler. Prolapsed Rectum and Risk Factors in Prader-Willi Syndrome: A Case-Based Review *J Pediatr Genet.* 2021 Mar 3;11(1):1-4. eCollection 2022 Mar.

**Abstract** A 14-year-old male adolescent patient with Prader-Willi syndrome (PWS) with maternal disomy 15 was reported with rectal prolapse as only the second patient in the literature. With predisposing risk factors present for rectal damage and prolapse in this syndrome, the incidence must be higher and therefore underreported. These risk factors include skin and rectal picking, self-stimulation, altered pain sensation, decreased muscle mass, strength and physical activity with hypotonia, and gastrointestinal (GI) disturbances. Pertinent literature was reviewed and analyzed that focused on clinical features and behavior seen in PWS as underrecognized risk factors for developing rectal damage and prolapse. An illustrative case is presented as the second patient reported with PWS and a prolapsed rectum. A discussion of predisposing behavioral and clinical risk factors is presented including for self-stimulation, rectal picking, chronic constipation, decreased gut motility, reduced water intake, and a restricted diet. Although a paucity of cases do exist, physical, behavioral, and GI findings common in PWS may contribute to rectal prolapse requiring better awareness and proactive surveillance, management, and treatment protocols for patients affected with this rare obesity-related genetic disorder. **Keywords:** Prader-Willi syndrome; chronic constipation; prolapsed; rectal picking; restricted diet; risk factors; self-injury.

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Jessica Duis , Lara C Pullen , Maria Picone Norman Friedman , Stephen Hawkins , Elise Sannar , Anna C Pfalzer Althea Robinson Shelton , Deepan Singh , Phyllis C Zee , Daniel G Glaze , Ameer Revana. Diagnosis and management of sleep disorders in Prader-Willi syndrome. *J Clin Sleep Med.* 2022 Feb 18. Online ahead of print.

**Abstract** Clinical experience and a growing body of evidence suggest that sleep disturbances are common in people with Prader-Willi syndrome (PWS). PWS is a rare neuroendocrine disorder characterized by early hypotonia and feeding difficulties; developmental delays; endocrinopathies; and behavioral concerns, especially rigidity, anxiety, and behavioral outbursts. PWS is also characterized by decreased resting energy expenditure and transition to hyperphagia and obesity. We propose that, for many people with PWS, clinical diagnosis and management of sleep disorders is an unmet need. We present current information to suggest disordered sleep is a significant burden for individuals with PWS and often overlooked. While central and obstructive sleep apnea are more widely recognized in PWS, other sleep disorders have increasingly gained recognition, including hypersomnia, narcolepsy-like phenotypes, and insomnia. Sleep disorders can impact behavior, cognition, and quality of life and health for individuals with PWS. Our goal is to bring sleep disorders to the forefront of therapeutic intervention for PWS patients. This paper presents a review of the literature and recommendations for clinical practice based on published research and our clinical experience as sleep specialists, geneticists, psychiatrists, pediatricians, otolaryngologists, and pulmonologists with extensive experience with this patient population. We recommend that management of sleep be considered an integral part of successful medical management of PWS. Further research concerning sleep problems in PWS is urgently needed to develop best practices and work toward a consensus statement for medical management to meet the needs of people with PWS.

**Keywords:** Prader-Willi syndrome; cataplexy; excessive daytime sleepiness; hypersomnolence; imprinting disorder; narcolepsy; obstructive sleep apnea; sleep-disordered breathing.

PMID: 35172921 DOI: 10.5664/jcsm.9938

Arianna Belli , Maria Breda, Chiara Di Maggio, Dario Esposito, Lavinia Marcucci, Oliviero Bruni. Children with neurodevelopmental disorders: how do they sleep? *Curr Opin Psychiatry.* 2022 Feb 14. Online ahead of print.

**Abstract** Purpose of review: In this review we summarized the available evidence on sleep disorders in children with neurodevelopmental disorders (NDDs) in particular: intellectual disability (including some genetic conditions such as Prader-Willi Syndrome, Smith-Magenis Syndrome), Autism spectrum

disorder, attention-deficit/hyperactivity disorder (ADHD), Developmental Coordination Disorder, language disorders, and specific learning disorders.

Recent findings: Children with NDDs frequently suffer from sleep disturbances, with a higher prevalence than that of the general pediatric population.

Summary: These problems tend to be chronic and may cause additional cognitive and behavioral difficulties, often affecting the whole family's well-being. Sleep behaviors are also related to other important developmental skills, such as attention and listening. Investigating sleep disorders in children with NDDs is therefore crucial in clinical practice. For a systematic approach in clinical practice, we propose the use of a short and easy to remember sleep screening tool

PMID: 35165244 DOI: 10.1097/YCO.0000000000000790

Berrin Ergun-Longmire, Minh H N Nguyen, Gulnur Com. Electrical status epilepticus during sleep in a child with Prader-Willi syndrome: a case report. *AME Case Rep.* 2022 Jan 25;6:7. eCollection 2022.

**Abstract** Prader-Willi syndrome (PWS) is a rare and complex genomic imprinting disorder caused by an absence of expression of paternal genes from chromosome 15q11.2-q13. Clinical manifestations of PWS depends on age. In early infancy, PWS patients is characterized by hypotonia and failure to thrive. Later in life, they can also exhibit hyperphagia, obesity, short stature, hypogonadism, behavioral issues and cognitive disability. Multiple sleep abnormalities including obstructive and/or central sleep apnea, daytime hypersomnolence, and impaired responses to hypercapnia and hypoxia have been described in patients with PWS. Recent studies also demonstrated an increased risk of seizures in PWS patients. Electrical status epilepticus in sleep (ESES) is an age-limited epilepsy with various seizure types, neurophysiological and motor impairment. The classic electroencephalogram (EEG) pattern of ESES involves continuous epileptic activity at 2-3 Hz occupying greater than 85% of non-rapid eye movement (REM) sleep. Treatment of the ESES syndrome consists of anti-epileptic drugs in routine cases, and corticosteroids, gamma globulins, the ketogenic diet, and surgery in refractory cases. In this project, we describe ESES during polysomnography in a 5-year-old female with PWS and no history of seizure disorder. To the best of our knowledge, this is the first case report on ESES in a PWS patient.

Keywords: Electrical status epilepticus in sleep (ESES); Prader-Willi syndrome (PWS); case report; polysomnography; seizure.

PMID: 35128315 PMCID: PMC8762383 DOI: 10.21037/acr-21-34

David G Ingram, Jill M Arganbright, Kelsee L Halpin, Caroline Okorie. Sleep Challenges in Children with Prader-Willi Syndrome: A Patient and Family Handout. *ATS Sch.* 2021 Dec 17;2(4):665-668. eCollection 2021 Dec.

PMID: 35079744 PMCID: PMC8749009 DOI: 10.34197/ats-scholar.2021-0025PE

Roberta Zerlotin, Angela Oranger, Patrizia Pignataro, Manuela Dicarolo, Filippo Maselli, Giorgio Mori, Silvia Concetta Colucci, Maria Grano Graziana Colaianni. Irisin and Secondary Osteoporosis in Humans *Int J Mol Sci.* 2022 Jan 8;23(2):690.

**Abstract** Irisin is a peptide secreted by skeletal muscle following exercise that plays an important role in bone metabolism. Numerous experiments in vitro and in mouse models have shown that the administration of recombinant irisin promotes osteogenesis, protects osteocytes from dexamethasone-induced apoptosis, prevents disuse-induced loss of bone and muscle mass, and accelerates fracture healing. Although some aspects still need to be elucidated, such as the dose- and frequency-dependent effects of irisin in cell cultures and mouse models, ample clinical evidence is emerging to support its physiological relevance on bone in humans. A reduction in serum irisin levels, associated with an increased risk of osteoporosis and bone fractures, was observed in postmenopausal women and in both men and women during aging. Recently, cohort studies of subjects with secondary osteoporosis showed that these patients have lower circulating levels of irisin, suggesting that this myokine could be a novel marker to monitor bone quality in this disease. Although there are still few studies, this review discusses the emerging data that are highlighting the involvement of irisin in some diseases that cause secondary osteoporosis.

Keywords: Cushing's disease; Prader-Willi syndrome; growth hormone; hyperparathyroidism; inflammatory bowel disease; irisin; osteoporosis  
PMID: 35054874 DOI: 10.3390/ijms23020690

## Behaviour

Catherine S Choong, Gillian M Nixon, A Marie Blackmore, Wai Chen, Peter Jacoby, Helen Leonard, Antony R Lafferty, Geoff Ambler, Nitin Kapur, Philip B Bergman, Cara Schofield, Chris Seton, Andrew Tai, Elaine Tham, Komal Vora, Patricia Crock, Charles Verge, Yassmin Musthaffa, Greg Blecher, Andrew Wilson, Jenny Downs. Daytime sleepiness and emotional and behavioral disturbances in Prader-Willi syndrome. *Eur J Pediatr.* 2022 Mar 22. Online ahead of print.

**Abstract** Individuals with Prader-Willi syndrome (PWS) often have excessive daytime sleepiness and emotional/behavioral disturbances. The objective of this study was to examine whether daytime sleepiness was associated with these emotional/behavioral problems, independent of nighttime sleep-disordered breathing, or the duration of sleep. Caregivers of individuals with PWS (aged 3 to 25 years) completed the Pediatric Sleep Questionnaire (PSQ), Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), and the parent version of the Developmental Behavior Checklist (DBC-P). Sleep adequacy was adjusted for age by computing sleep duration against age-specific recommendations. The associations between ESS-CHAD and the total DBC and its subscale scores were evaluated by linear regression, adjusted for sleep-related breathing difficulties, sleep adequacy, and body mass index (BMI). There were 54 responses for individuals with PWS (including 22 males) aged 4.4-24.0 (mean 12.5) years. Daytime sleepiness predicted a substantial proportion of the variance in total DBC-P scores in the unadjusted model (28%;  $\beta = 0.028$ ;  $p < 0.001$ ) and when adjusted for sleep adequacy, BMI, and sleep-related breathing difficulties (29%;  $\beta = 0.023$ ;  $p = 0.007$ ). This relationship was not moderated by BMI Z-scores, but the relationship was more prominent for children younger than 12 years than for children older than 12 years. **Conclusions:** These findings provide preliminary novel evidence that daytime sleepiness may drive the expression of emotional/behavioral disturbances, and should be explored as a potential modifiable risk factor for these disturbances in PWS, particularly pre-adolescent children. **Keywords:** Genetic disorder; Intellectual disability; Mental health; Sleepiness.  
PMID: 35316366 DOI: 10.1007/s00431-022-04439-2

Meritxell Fernández-Lafitte, Jesus Cobo, Ramon Coronas, Isabel Parra, Joan Carles Oliva, Aida Álvarez, Susanna Esteba-Castillo, Olga Giménez-Palop, Diego J Palao, Assumpta Caixàs. Social Responsiveness and Psychosocial Functioning in Adults with Prader-Willi Syndrome. *J Clin Med.* 2022 Mar 5;11(5):1433.

**Abstract** Although various studies have investigated symptoms of autism spectrum disorder (ASD) in Prader-Willi syndrome (PWS), little is known about the consequences of these symptoms, especially in psychosocial function. We aimed to explore ASD symptoms in adults with PWS with special attention to psychosocial functionality. This cross-sectional study included 26 adults (15 women) with PWS who attended a reference unit for rare diseases. Participants' primary caregivers completed the Social Responsiveness Scale (SRS), and clinicians assessed multidimensional functioning with the Personal and Social Performance Scale (PSP). Impaired social responsiveness was identified in 20 (76.9%) participants, and manifest to marked difficulties in social functioning were identified in 13 (50%). Participants with impaired social responsiveness ( $SRS \geq 60$ ) had significantly worse scores in functionality measured with the PSP ( $U = 12.5$ ;  $p = 0.009$ ) and with three of the four PSP main areas. Moreover, scores for the *Social Cognition* domain of the SRS correlated positively with the *Socially useful activities* ( $p < 0.05$ ) and *Personal and social relationships* ( $p < 0.01$ ) main areas of the PSP.

These results suggest that difficulties in social skills should be assessed in all psychosocial evaluations of patients with PWS.

Keywords: Prader–Willi syndrome; autism; autism spectrum disorders; function; functionality; social function; social responsiveness.

PMID: 35268524 PMID: PMC8911114 DOI: 10.3390/jcm11051433

Anthony Holland , Katie Manning. t-VNS to treat disorders of behaviour in Prader-Willi Syndrome and in people with other neurodevelopmental conditions. *Auton Neurosci.* 2022 Feb 12;239:102955. Online ahead of print.

**Abstract** This paper proposes that tVNS has the potential to be a new treatment for some of the behaviour difficulties that may affect people with intellectual disabilities and/or autism, particularly those people born with specific neurodevelopmental syndromes. Behaviours, such as emotional outbursts, physical aggression, and self-injury are a relative common occurrence in these groups and have a significant impact on wellbeing and quality of life for the individuals and their families. Such behaviours have generally been understood through the lens of learning theory, the likelihood of their occurrence being shaped and reinforced by the responses of others. However, when vagus nerve stimulation has been used to treat epilepsy improvements in cognition, behaviour, and general wellbeing have been noted suggesting that with these behaviours other causal mechanisms are also important. More recently incidental findings from a proof of concept study where vagus nerve stimulation was given, using an implanted device, to people with the genetically determined neurodevelopmental disorder, Prader-Willi Syndrome (PWS), findings of benefit supported the above view. A second study, this time using tVNS, reported a similar result. In this paper we review the evidence for the use of tVNS for behavioural problems, consider the challenges when conducting trials in this population, and reflect on what the preliminary observations in people with PWS tell us about the possible mechanisms that underpin such behaviours.

Keywords: Autism spectrum conditions; Challenging behaviour; Neurodevelopmental disorders; Prader-Willi syndrome; Vagus nerve stimulation.

PMID: 35219158 DOI: 10.1016/j.autneu.2022.102955

Rocío Arias-Del Razo , Maria de Lourdes Velasco Vazquez , Petru Turcanu , Mathieu Legrand , Maeva Floch , Tamara A R Weinstein , Leana R Goetze , Sara M Freeman , Alexander Baxter , Lynea R Witczak , Elizabeth Sahagún , Trish Berger , Suma Jacob , Rebecca H Lawrence , Emily S Rothwell , Logan E Savidge , Marjorie Solomon , Sally P Mendoza , Karen L Bales. Long term effects of chronic intranasal oxytocin on adult pair bonding behavior and brain glucose uptake in titi monkeys (*Plecturocebus cupreus*). *Horm Behav.* 2022 Feb 2;140:105126. Online ahead of print.

**Abstract** Intranasal oxytocin (IN OXT) administration has been proposed as a pharmacological treatment for a range of biomedical conditions including neurodevelopmental disorders. However, studies evaluating the potential long-lasting effects of chronic IN OXT during development are still scarce. Here we conducted a follow-up study of a cohort of adult titi monkeys that received intranasal oxytocin 0.8 IU/kg (n = 15) or saline (n = 14) daily for six months during their juvenile period (12 to 18 months of age), with the goal of evaluating the potential long-lasting behavioral and neural effects one year post-treatment. Subjects were paired with an opposite-sex mate at 30 months of age (one year post-treatment). We examined pair affiliative behavior in the home cage during the first four months and tested for behavioral components of pair bonding at one week and four months post-pairing. We assessed long-term changes in brain glucose uptake using <sup>18</sup>FDG positron emission tomography (PET) scans. Our results showed that OXT-treated animals were more affiliative across a number of measures, including tail twining, compared to SAL treated subjects (tail twining is considered the "highest" type of affiliation in titi monkeys). Neuroimaging showed no treatment differences in glucose uptake between SAL and OXT-treated animals; however, females showed higher glucose uptake in whole brain at 23 months, and in both the whole brain and the social salience network at 33 months of age compared to males. Our results suggest that chronic IN OXT administration during development can have long-term effects on adult social behavior.

Keywords: Autism; Behavior; Intranasal oxytocin; PET scan; Prader-Willi syndrome.

PMID: 3512310 DOI: 10.1016/j.yhbeh.2022.105126

Jenny Downs , A Marie Blackmore , Wai Chen , Gillian M Nixon , Catherine S Choong. Strengths and challenging behaviors in children and adolescents with Prader-Willi syndrome: Two sides to the coin. *Am J Med Genet A*. 2022 Jan 29. Online ahead of print.

**Abstract** Prader-Willi Syndrome (PWS) is a rare genetic disorder associated with emotional/behavioral disturbances. These difficulties are well documented in the literature, but the positive attributes of these individuals are not described. Taking a strengths-based approach, the aim of this study was to describe the emotional/behavioral strengths and difficulties in children and young people with PWS from their parent caregivers' perspectives. Parent caregivers of 52 individuals with PWS aged 4-24 years (median = 12.1 years; including 22 males) completed the parent form of the Developmental Behavior Checklist (DBC-P), including its original two open-ended questions regarding positive traits. Prevalences of emotional/behavioral disturbances were comparable to those reported in previous literature: common behaviors of concern across studies being skin-picking (75%), impulsivity (69%), poor sense of danger (67%), lying (67%), and tantrums (54%). Total DBC-P scores showed that just over half (n = 28, 54%) had scores indicative of clinically significant behavior problems. However, thematic analysis of caregivers' written comments regarding their children's strengths resolved into three themes: warmth (94%), persistence (41%), and skills (41%). Warmth encompassed friendliness, happiness, and empathy. A strength-based approach to behavioral difficulties in PWS provides a more balanced view of the children and a more holistic foundation for interventions.

Keywords: Prader-Willi syndrome; behavior disturbance; strengths-based.

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Sung Yoon Cho , Danbee Kang , Minji Im , Aram Yang , Min-Sun Kim , Jiyeon Kim , , Eun Kyung Kwon , Eu Jin Choi , Sunju Han , Young Ah Park , Min Jung Kwak , Youngha Kim , Juhee Cho , Dong-Kyu Jin. *Epidemiol Health*. 2022 Jan 10;e2022014. Online ahead of print.

**Abstract** Objectives: Hyperphagia is a highly stressful, life-threatening feature of Prader-Willi Syndrome (PWS). It is important to assess this complex behavior accurately over time. This study aims to develop and validate the Pediatric-Youth Hyperphagia Assessment tool for children and adolescents with PWS.

Methods: After the extensive literature review and qualitative interviews, the final version of the Pediatric-Youth Hyperphagia Assessment for PWS (PYHAP) with 14 questions in three domains [verbal (5), behavior (4), and social (5)] was developed and tested at Samsung Medical Center in Seoul, Korea from July 2018 and September 2019. Exploratory and confirmatory factor analysis (CFA) were performed to confirm construct validity. The correlation between the PYHAP and the Korean Children's Eating Behavior Questionnaire (K-CEBQ) were calculated to evaluate the convergent and discriminant validity. Criterion validity and validity of the response categories were also tested.

Results: Cronbach's alpha coefficient of the PYHAP was 0.92. The fit indices for CFA were good (CFI = 0.87; SRMR = 0.08). Domains of the PYHAP were highly correlated with relevant domains of the K-CEBQ. The accuracy of the PYHAP score to predict uncontrolled hyperphagia was good (AUC = 0.75, 95% CI = 0.65, 0.85).

Conclusion: The PYHAP was a reliable and valid tool to evaluate hyperphagia in children and adolescents with PWS via the caregivers' assessments. It is recommended to use the PYHAP as a tool to communicate with parents or caregivers about hyperphagia of the patients or to monitor and manage extreme behaviors of children with PWS.

Keywords: Appetite; Eating disorder; Hyperphagia; Obesity; Prader-Willi syndrome; Questionnaire

PMID: 35038830 DOI: 10.4178/epih.e2022014

## Cognition and mental health



Emily Shelkowitz , Marie G Gantz , Ty A Ridenour , Ann O Scheimann , Theresa Strong , Jessica Bohonowych , Jessica Duis. Neuropsychiatric features of Prader-Willi syndrome. *Am J Med Genet A*. 2022 Jan 30. Online ahead of print.

**Abstract** Prader-Willi syndrome (PWS) is a genetic disorder characterized by hypotonia and poor feeding in infancy which progresses to hyperphagia in early-mid childhood, as well as developmental delays, a spectrum of behavioral and psychiatric concerns, endocrinopathies, orthopedic issues, and less commonly, seizures, sleep apnea, and narcolepsy with or without cataplexy. This study used data in the Global PWS Registry (N = 893) to explore the onset and severity over time of the neuropsychiatric features reported in individuals with PWS and explored its associations with sleep disorders, seizures, and psychiatric symptoms. Results demonstrate that seizures are more common in the deletion subtype and that narcolepsy and cataplexy are more common in individuals who have sleep-related seizures. Finally, this work shows that anxiety and compulsive behaviors are persistent features of PWS that may arise early in childhood, and that anxiety is associated with higher frequency of other comorbid psychiatric diagnoses. In conclusion, this study is one of the largest to date characterizing sleep disorders and neuropsychiatric characteristics of individuals with PWS and reports on the novel association between sleep disorders and seizures. This study is also one of the first to offer details on the nature of the progression of these features in individuals with PWS.

Keywords: Prader-Willi syndrome; anxiety; narcolepsy; neuropsychiatric; seizures

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