PWS publications Jul to Sept 2019

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st July and end of September 2019 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. Open access is indicated next to the link.

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 tel. +44 (0)1223 465266)

PWS publications 1st July to 30th Sept 2019

Index

General PWS and families

Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. Genes (Basel). 2019 Sep 14;10(9). pii: E713.

Mao SJ, Shen J, Xu F, Zou CC. Quality of life in caregivers of young children with Prader-Willi syndrome. World J Pediatr. 2019 Sep 13.. [Epub ahead of print]

Demir K, Konakçı E, Özkaya G, Kasap Demir B, Özen S, Aydın M, Darendeliler F. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations J Clin Res Pediatr Endocrinol. 2019 Sep 2.. [Epub ahead of print]

Butler MG, Miller JL, Forster JL. Prader-Willi Syndrome - Clinical Genetics, Diagnosis and Treatment Approaches: An Update. Curr Pediatr Rev. 2019 Jul 16.. [Epub ahead of print]

Sävendahl L, Polak M, Backeljauw P Blair J, Miller BS, Rohrer TR, Pietropoli A, Ostrow V, Ross J Treatment of Children with Growth Hormone in the US and Europe: Long-term Follow-up from NordiNet IOS and ANSWER Program. J Clin Endocrinol Metab. 2019 Jul 15. pii: jc.2019-00775.. [Epub ahead of print].

Mackay J, McCallum Z, Ambler GR, Vora K, Nixon G, Bergman P, Shields N, Milner K, Kapur N, Crock P, Caudri D, Curran J, Verge C, Seton C, Tai A, Tham E, Musthaffa Y, Lafferty AR, Blecher G, Harper J, Schofield C, Nielsen A, Wilson A, Leonard H, Choong CS, Downs J. Requirements for improving health and well-being of children with Prader-Willi syndrome and their families. J Paediatr Child Health. 2019 Jun 30.. [Epub ahead of print]

Genetics and brain imaging

Colovati MES, Grossi BM, Nunes GD, Fock RA, Guedes DR, Melaragno MI, Cernach MCSP. Atypical Prader-Willi and 15q13.3 Microdeletion Syndromes in a Patient with an Unbalanced Translocation. Cytogenet Genome Res. 2019 Aug 9.. [Epub ahead of print]

Wang SE, Jiang YH. Potential of Epigenetic Therapy for Prader-Willi Syndrome. Trends Pharmacol Sci. 2019 Jul 25. pii: S0165-6147(19)30139-7. [Epub ahead of print]

Babbs RK, Beierle JA, Ruan QT, Kelliher JC, Chen MM, Feng AX, Kirkpatrick SL, Benitez FA, Rodriguez FA, Pierre JJ, Anandakumar J, Kumar V, Mulligan MK, Bryant CD. *Cyfip1* Haploinsufficiency Increases Compulsive-Like Behavior and Modulates Palatable Food Intake in Mice: Dependence on *Cyfip2* Genetic Background, Parent-of Origin, and Sex. G3 (Bethesda). 2019 Jul 19. pii: g3.400470.2019.. [Epub ahead of print]

Iourov IY, Vorsanova SG, Zelenova MA, Vasin KS, Kurinnaia OS, Korostelev SA, Yurov YB. [Epigenomic variations manifesting as a loss of heterozygosity affecting imprinted genes represent a molecular mechanism of autism spectrum disorders and intellectual disability in children]. [Article in Russian; Abstract available in Russian from the publisher] Zh Nevrol Psikhiatr Im S S Korsakova. 2019;119(5):91-97..

Ge MM, Gao YY, Wu BB, Yan K, Qin Q, Wang H, Zhou W, Yang L Relationship between phenotype and genotype of 102 Chinese newborns with Prader-Willi syndrome. Mol Biol Rep. 2019 Jul 3.. [Epub ahead of print]

Chen W, Xu D, Ma C, Zhang C, Li J, Zhang W, Zhao G, Li S. The molecular structure and imprinting status of the IPW (imprinted gene in the Prader-Willi syndrome region) gene in cattle. Anim Genet. 2019 Jul 3. [Epub ahead of print]

Endocrine including GH

Yang A, Choi JH, Sohn YB, Eom Y, Lee J, Yoo HW, Jin DK. Effects of recombinant human growth hormone treatment on growth, body composition, and safety in infants or toddlers with Prader-Willi syndrome: a randomized, active-controlled trial. Orphanet J Rare Dis. 2019 Sep 11;14(1):216.

Palmieri VV, Lonero A, Bocchini S, Cassano G, Convertino A, Corica D, Crinò A, Fattorusso V, Ferraris S, Fintini D, Franzese A, Grugni G, Iughetti L, Lia R, Macchi F, Madeo SF, Matarazzo P, Nosetti L, Osimani S, Pajno R, Patti G, Pellegrin MC, Perri A, Ragusa L, Rutigliano I, Sacco M, Salvatoni A, Scarano E, Stagi S, Tornese G, Trifirò G, Wasniewska M, Fischetto R, Giordano P, Licenziati MR, Delvecchio M; Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Uniparental disomy and pretreatment IGF-1 may predict elevated IGF-1 levels in Prader-Willi patients on GH treatment. Growth Horm IGF Res. 2019 Aug 28;48-49:9-15.. [Epub ahead of print]

Laumonerie P, Tibbo ME, Ibnoulkhatib A, Kerezoudis P, Diene G, Thevenin Lemoine C, Accadbled F, Sales de Gauzy J. Evolution of Hip Dysplasia in Pediatric Patients With Prader-Willi Syndrome Treated With Growth Hormone Early in Development. J Pediatr Orthop. 2019 Aug 30. [Epub ahead of print]

Braxton TM, Sarpong DE, Dovey JL, Guillou A, Evans B, Castellano JM, Keenan BE, Baraghithy S, Evans SL, Tena-Sempere M, Mollard P, Tam J, Wells T. Thermoneutrality improves skeletal impairment in adult Prader-Willi syndrome mice. J Endocrinol. 2019 Aug 1. pii: JOE-19-0279.R1.. [Epub ahead of print

Donze SH, Hokken-Koelega ACS. Reply to Commentary on 'Prevalence of growth hormone (GH) deficiency in previously GH treated young adults with Prader-Willi syndrome'. Clin Endocrinol (Oxf). 2019 Jul 23.. [Epub ahead of print]

Deng L, Wang R, Li H, Zhang C, Zhao L, Zhang M. miRNA-Gene Regulatory Network in Gnotobiotic Mice Stimulated by Dysbiotic Gut Microbiota Transplanted From a Genetically Obese Child. Front Microbiol. 2019 Jul 5;10:1517.. eCollection 2019.

Canning DA. Re: Orchidopexy in Children with Prader-Willi Syndrome: Results of a Long-Term Follow-up Study. J Urol. 2019 Jul 9:10109701JU000057701264888f4.. [Epub ahead of print]

Corripio R, Tubau C, Calvo L, Brun C, Capdevila N, Larramona H, Gabau E. Safety and effectiveness of growth hormone therapy in infants with Prader-Willi syndrome younger than 2 years: a prospective study. J Pediatr Endocrinol Metab. 2019 Jul 4. pii: /j/jpem.ahead-of-print/jpem-2018-0539/jpem-2018-0539.xml. . [Epub ahead of print]

Sensory and physical

Liu SY, Wong SK, Lam CC, Ng EK. Bariatric surgery for Prader-Willi syndrome was ineffective in producing sustainable weight loss: Long term results for up to 10 years. Pediatr Obes. 2019 Sep 12. [Epub ahead of print]

Demir K, Konakçı E, Özkaya G, Kasap Demir B, Özen S, Aydın M, Darendeliler F. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations J Clin Res Pediatr Endocrinol. 2019 Sep 2.. [Epub ahead of print]

Laumonerie P, Tibbo ME, Ibnoulkhatib A, Kerezoudis P, Diene G, Thevenin Lemoine C, Accadbled F, Sales de Gauzy J. Evolution of Hip Dysplasia in Pediatric Patients With Prader-Willi Syndrome Treated With Growth Hormone Early in Development. J Pediatr Orthop. 2019 Aug 30.. [Epub ahead of print]

Lima FCB, do Nascimento Junior EB, Teixeira SS, Coelho FM, Oliveira GDP. Thinking outside the box: cataplexy without narcolepsy. Sleep Med. 2019 Mar 20. pii: S1389-9457(19)30068-1.. [Epub ahead of print]

Oore J, Connell B, Yaszay B, Samdani A, Hilaire TS, Flynn T, El-Hawary R; Children's Spine Study Group; Growing Spine Study Group. Growth Friendly Surgery and Serial Cast Correction in the Treatment of Early-onset Scoliosis for Patients With Prader-Willi Syndrome. J Pediatr Orthop. 2019 Sep;39(8):e597-e601.

Salvatoni A, Moretti A, Grugni G, Agosti M, Azzolini S, Bonaita V, Cianci P, Corica D, Crinò A, Delvecchio M, Ferraris S, Greggio NA, Iughetti L, Licenziati MR, Madeo SF, Nosetti L[1]Pajno R, Rutigliano I, Sacco M, Salvatore S, Scarano E, Trifirò G, Wasniewska M. Anthropometric characteristics of newborns with Prader-Willi syndrome. Am J Med Genet A. 2019 Jul 30.. [Epub ahead of print]

Manzardo AM, Heinemann J, McManus B, Loker C, Loker J, Butler MG. Venous Thromboembolism in Prader-Willi Syndrome: A Questionnaire Survey. Genes (Basel). 2019 Jul 19;10(7). pii: E550..

Bantim YCV, Kussaba ST, de Carvalho GP, Garcia-Junior IR, Roman-Torres CVG. Oral health in patients with Prader-Willi syndrome: current perspectives. Clin Cosmet Investig Dent. 2019 Jul 4;11:163-170.. eCollection 2019.

Behaviour

Kimonis V, Surampalli A, Wencel M, Gold JA, Cowen NM. A randomized pilot efficacy and safety trial of diazoxide choline controlled-release in patients with Prader-Willi syndrome PLoS One. 2019 Sep 23;14(9):e0221615.. eCollection 2019.

Kato E, Kimura M, Okuda T, Toyoda M, Fukagawa M. Behavior Modification Maintenance with Long-Term Blood Glucose and Weight Management in Prader-Willi Syndrome Complicated with Diabetes: Team Management Approach Combined with Pharmacological Treatment. Case Rep Med. 2019 Jul 8;2019:6129019.. eCollection 2019.

Devine DP. Animal Models of Self-Injurious Behavior: An Update. Methods Mol Biol. 2019;2011:41-60.

Cognition and mental health

Dimitropoulos A, Zyga O, Russ SW. Early Social Cognitive Ability in Preschoolers with Prader-Willi Syndrome and Autism Spectrum Disorder. J Autism Dev Disord. 2019 Aug 6.. [Epub ahead of print]

Estival S, Krasny-Pacini A, Laurier V, Maugard C, Thuilleaux D, Postal V. Cognitive Training Targeting Planning Dysfunction in Adults with Prader-Willi Syndrome: Brief Report of a Study Protocol.Dev Neurorehabil. 2019 Jul 29:1-7.. [Epub ahead of print]

Butler MG, Matthews NA, Patel N, Surampalli A, Gold JA, Khare M, Thompson T, Cassidy SB, Kimonis VE. Impact of genetic subtypes of Prader-Willi syndrome with growth hormone therapy on intelligence and body mass index. Am J Med Genet A. 2019 Jul 16. [Epub ahead of print]

Abstracts

General PWS and families

Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. Genes (Basel). 2019 Sep 14;10(9). pii: E713.
Abstract Advances in technologies offer new opportunities to collect and integrate data from a broad range of sources to advance the understanding of rare diseases and support the development of new treatments. Prader-Willi syndrome (PWS) is a rare, complex neurodevelopmental disorder, which has a variable and incompletely understood natural history. PWS is characterized by early failure to thrive, followed by the onset of excessive appetite (hyperphagia). Additional characteristics include multiple endocrine abnormalities, hypotonia, hypogonadism, sleep disturbances, a challenging neurobehavioral phenotype, and cognitive disability. The Foundation for Prader-Willi Research's Global PWS Registry is one of more than twenty-five registries developed to date through the National Organization of Rare Disorders (NORD) IAMRARE Registry Program. The Registry consists of surveys covering general medical history, system-specific clinical complications, diet, medication and supplement use, as well as behavior, mental health, and social information. Information is primarily parent/caregiver entered. The platform is flexible and allows addition of new surveys, including updatable and longitudinal surveys. Launched in 2015, the PWS Registry has enrolled 1696 participants from 37 countries, with 23,550 surveys completed. This resource can improve the understanding of PWS natural history and support medical product development for PWS.
KEYWORDS: Prader–Willi syndrome; natural history; registry
PMID:31540108 DOI:10.3390/genes10090713


Mao SJ, Shen J, Xu F, Zou CC. Quality of life in caregivers of young children with Prader-Willi syndrome. World J Pediatr. 2019 Sep 13.. [Epub ahead of print]
Abstract BACKGROUND: This study aimed to measure quality of life (QOL) in primary caregivers of young childrenwith Prader-Willi syndrome (PWS).
METHODS: The caregivers of 32 children aged from 6.1 to 71.2 months completed the Chinese version of the World Health Organization Quality of Life-BREF (WHOQOL-BREF). We also evaluated the social adaption capacity of these children with Infants-Junior Middle School Students' Social-Life Abilities Scale. Correlation test was used to explore the related factors to caregivers' QOL.
RESULTS: Caregivers of young children with PWS had significantly lower QOL. The correlation analyses revealed that caregivers' QOL was lower in children with young age, combined diseases or symptoms or poor social adaption, or caregivers having concerns about the child.
CONCLUSIONS: Rearing a chilld with PWS may lead to decreased QOL. Psychological status of caregivers should be highlighted and social support should be given to families with PWS children.
KEYWORDS: Caregiver Prader–Willi syndrome (PWS); Quality of life (QOL); Social adaption; WHOQOL-BREF
PMID:31520366 DOI:10.1007/s12519-019-00311-w


Demir K, Konakçı E, Özkaya G, Kasap Demir B, Özen S, Aydın M, Darendeliler F. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations J Clin Res Pediatr Endocrinol. 2019 Sep 2.. [Epub ahead of print]

Abstract Many new features have recently been incorporated to ÇEDD Çözüm / Child Metrics, an online and freely accessible scientific toolset. Various auxological assessments can now be made with data of children with genetic diseases (Prader Willi syndrome, Noonan syndrome, Turner syndrome, Down syndrome, and Achondroplasia) and preterm and term newborns. More detailed reports for height, weight, and body mass index (BMI) data of a given child are now available. Last but not least, office and 24-hour ambulatory blood pressure values can be analyzed according to normative data.
KEYWORDS: Application; mobile; calculator; short stature; growth chart; hypertension; guideline; AAP
PMID:31475511 DOI:10.4274/jcrpe.galenos.2019.2019.0127

Butler MG, Miller JL, Forster JL. Prader-Willi Syndrome - Clinical Genetics, Diagnosis and Treatment Approaches: An Update. Curr Pediatr Rev. 2019 Jul 16.. [Epub ahead of print]

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a neurodevelopmental genomic imprinting disorder with lack of expression of genes inherited from the paternal chromosome 15q11-q13 region usually from paternal 15q11-q13 deletions (about 60%) or maternal uniparental disomy 15 or both 15s from the mother (about 35%). An imprinting center controls the expression of imprinted genes in the chromosome 15q11-q13 region. Key findings include infantile hypotonia, a poor suck, failure to thrive and hypogonadism/hypogenitalism. Short stature and small hands/feet due to growth and other hormone deficiencies, hyperphagia and marked obesity occurs in early childhood, if uncontrolled. Cognitive and behavioral problems (tantrums, compulsions, compulsive skin picking) are common.
OBJECTIVE: Hyperphagia and obesity with related complications are major causes of morbidity and mortality in PWS. This report will describe an accurate diagnosis with determination of specific genetic subtypes, appropriate medical management, and best practice treatment approaches.
METHODS AND RESULTS: An extensive literature review was undertaken related to genetics, clinical findings and laboratory testing, clinical and behavioral assessments and summary of updated health-related information addressing the importance of early PWS diagnosis and treatment. A searchable, bulleted and formatted list of topics is provided utilizing a Table of Contents approach for the clinical practitioner.
CONCLUSIONS: Physicians and other health care providers can use this review with clinical, genetic and treatment summaries divided into sections pertinent in the context of clinical practice. Frequently asked questions by clinicians, families and other interested participants or providers will be addressed.
.KEYWORDS: Diagnostic protocols and treatment approaches; Prader-Willi syndrome; caloric intake; genetic testing; genetics clinical description of Prader-Willi syndrome; genomic imprinting; medication and care management; obesity
PMID:31333129 DOI:10.2174/1573396315666190716120925

Sävendahl L, Polak M, Backeljauw P Blair J, Miller BS, Rohrer TR, Pietropoli A, Ostrow V, Ross J Treatment of Children with Growth Hormone in the US and Europe: Long-term Follow-up from NordiNet IOS and ANSWER Program. J Clin Endocrinol Metab. 2019 Jul 15. pii: jc.2019-00775.. [Epub ahead of print].

Abstract CONTEXT: Understanding real-world prescribing of growth hormone (GH) may help improve treatment of eligible patients.
OBJECTIVE: Overall: to assess real-world effectiveness and safety of GH (Norditropin). This analysis: to compare clinical characteristics of GH-treated children in the USA and Europe.
DESIGN: ANSWER (2002-2016, USA) and NordiNet IOS (2006-2016, Europe) were multicenter longitudinal observational cohort studies.
SETTING: Data were recorded in 207 (USA) and 469 (Europe) clinics.

PARTICIPANTS: Patients with GH deficiency, Turner syndrome, Noonan syndrome, idiopathic short stature, Prader-Willi Syndrome, or born small for gestational age, who commenced GH treatment aged <1 year.
INTERVENTION: GH was prescribed by treating physicians according to local practice.
MAIN OUTCOMES MEASURE(S): Baseline data and drug doses were recorded. Data on effectiveness and safety were collected.
RESULTS: ANSWER had 19,847 patients in the full analysis set (FAS; patients with birthdate information and ≥1 GH prescription) and 12,660 in the effectiveness analysis set (EAS; GH-naïve patients with valid baseline information). NordiNet IOS had 17,711 (FAS) and 11,967 (EAS). Boys accounted for 69% (ANSWER) and 57% (NordiNet IOS). Treatment start occurred later than optimal to improve growth. The proportion of boys treated was generally larger, children were older at treatment start, and GH doses were higher in the USA vs Europe. No new safety signals of concern were noted.
CONCLUSIONS: In most indications, more boys than girls were treated, and treatment started late. Earlier diagnosis of GH-related disorders is needed. The data support a favorable benefit-risk profile of GH therapy in children.
PMID:31305924 DOI:10.1210/jc.2019-00775

Mackay J, McCallum Z, Ambler GR, Vora K, Nixon G, Bergman P, Shields N, Milner K, Kapur N, Crock P, Caudri D, Curran J, Verge C**,** Seton C, Tai A, Tham E, Musthaffa Y, Lafferty AR, Blecher G, Harper J, Schofield C, Nielsen A, Wilson A, Leonard H, Choong CS, Downs J. Requirements for improving health and well-being of children with Prader-Willi syndrome and their families. J Paediatr Child Health. 2019 Jun 30.. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is a rare genetic condition with multi-system involvement. The literature was reviewed to describe neurodevelopment and the behavioural phenotype, endocrine and metabolic disorders and respiratory and sleep functioning. Implications for child and family quality of life were explored. Challenging behaviours contribute to poorer well-being and quality of life for both the child and caregiver. Recent evidence indicates healthy outcomes of weight and height can be achieved with growth hormone therapy and dietary restriction and should be the current target for all individuals with PWS. Gaps in the literature included therapies to manage challenging behaviours, as well as understanding the effects of growth hormone on respiratory and sleep function. New knowledge regarding the transition of children and families from schooling and paediatric health services to employment, accommodation and adult health services is also needed. Developing a national population-based registry could address these knowledge gaps and inform advocacy for support services that improve the well-being of individuals with PWS and their families.

KEYWORDS: Prader-Willi syndrome; endocrine; hyperphagia; quality of life; sleep disordered breathing
PMID:31257692 DOI:10.1111/jpc.14546

Genetics and brain imaging

Colovati MES, Grossi BM, Nunes GD, Fock RA, Guedes DR, Melaragno MI, Cernach MCSP. Atypical Prader-Willi and 15q13.3 Microdeletion Syndromes in a Patient with an Unbalanced Translocation. Cytogenet Genome Res. 2019 Aug 9.. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) and recurrent 15q13.3 microdeletion syndrome can be caused by genomic rearrangements in the complex 15q11q13 chromosomal region. Here, we describe the first female child with PWS and 15q13.3 microdeletion syndrome resulting from an unusual 10.7-Mb deletion from 15pter to 15q13.3 due to an unbalanced de novo 15;19 translocation. The patient presents with hypotonia, microcephaly, developmental delay with lack of speech, intellectual disability, happy demeanor, clinodactyly of the 4th and 5th fingers, and dysmorphic facial features discordant for PWS and consistent with an atypical phenotype.
KEYWORDS: 15;19 translocation; 15q deletion; 15q13.3 microdeletion syndrome; Prader-Willi syndrome
PMID:31394532 DOI:10.1159/000501753

Wang SE, Jiang YH. Potential of Epigenetic Therapy for Prader-Willi Syndrome. Trends Pharmacol Sci. 2019 Jul 25. pii: S0165-6147(19)30139-7. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is a neurobehavioral and epigenetic disorder caused by the deficiency of paternally expressed genes in the chromosome 15q11-q13. This unique molecular defect renders PWS an exciting opportunity to explore epigenetic therapy. Here, we briefly highlight recent findings from small molecule screening and CRISPR/Cas9-mediated epigenome editing that offer promising therapeutic options along with the challenges that remain in developing a successful epigenetic therapy for PWS in humans.
KEYWORDS: CRISPR/Cas9 mediated epigenome editing; G9a/EHMT2 inhibitor; Prader-Willi syndrome (PWS); epigenetic therapy; genomic imprinting; small molecules
PMID:31353046 DOI:10.1016/j.tips.2019.07.002

Babbs RK, Beierle JA, Ruan QT, Kelliher JC, Chen MM, Feng AX, Kirkpatrick SL, Benitez FA, Rodriguez FA, Pierre JJ, Anandakumar J, Kumar V, Mulligan MK, Bryant CD. *Cyfip1* Haploinsufficiency Increases Compulsive-Like Behavior and Modulates Palatable Food Intake in Mice: Dependence on *Cyfip2* Genetic Background, Parent-of Origin, and Sex. G3 (Bethesda). 2019 Jul 19. pii: g3.400470.2019.. [Epub ahead of print]
Abstract Binge eating (BE) is a heritable trait associated with eating disorders and involves episodes of rapid, large amounts of food consumption. We previously identified cytoplasmic FMR1-interacting protein 2 (*Cyfip2*) as a genetic factor underlying compulsive-like BE in mice. *CYFIP2* is a homolog of *CYFIP1* which is one of four paternally-deleted genes in patients with Type I Prader-Willi Syndrome (PWS), a neurodevelopmental disorder whereby 70% of cases involve paternal 15q11-q13 deletion. PWS symptoms include hyperphagia, obesity (if untreated), cognitive deficits, and obsessive-compulsive behaviors. We tested whether *Cyfip1* haploinsufficiency (+/-) would enhance compulsive-like behavior and palatable food (PF) intake in a parental origin- and sex-dependent manner on two *Cyfip2* genetic backgrounds, including the BE-prone C57BL/6N (*Cyfip2* $^{N/N}$) background and the BE-resistant C57BL/6J (*Cyfip2* $^{J/J}$) background. *Cyfip1* $^{+/-}$ mice showed increased compulsive-like behavior on both backgrounds and increased PF intake on the *Cyfip2* $^{N/N}$ background. In contrast, maternal *Cyfip1* haploinsufficiency on the BE-resistant *Cyfip2* $^{J/J}$ background induced a robust escalation in PF intake in wild-type *Cyfip1* $^{J/J}$ males while having no effect in *Cyfip1* $^{J/-}$ males. Notably, induction of behavioral phenotypes in wild-type males following maternal *Fmr1* $^{+/-}$ has previously been reported. In the hypothalamus, there was a paternally-enhanced reduction in CYFIP1 protein whereas in the nucleus accumbens, there was a maternally-enhanced reduction in CYFIP1 protein. No change in FMR1 protein (FMRP) was observed in *Cyfip1* $^{+/-}$ mice, regardless of parental origin. To summarize, *Cyfip1* haploinsufficiency increased compulsive-like behavior and induced genetic background-dependent, sex-dependent, and parent-of-origin-dependent effects on PF consumption and CYFIP1 expression that could have relevance for neurodevelopmental and neuropsychiatric disorders.
KEYWORDS: C57BL/6 substrains; FMRP; Fragile X; addiction genetics; anorexia nervosa; binge eating disorder; neuropsychiatric; overeating; psychiatric genetics

PMID:31324746 DOI:10.1534/g3.119.400470

Iourov IY, Vorsanova SG, Zelenova MA, Vasin KS, Kurinnaia OS, Korostelev SA, Yurov YB. [Epigenomic variations manifesting as a loss of heterozygosity affecting imprinted genes represent a molecular mechanism of autism spectrum disorders and intellectual disability in children]. [Article in Russian; Abstract available in Russian from the publisher] Zh Nevrol Psikhiatr Im S S Korsakova. 2019;119(5):91-97..

Abstract AIM: Long continuous stretches of homozygosity (LCSH) are regularly detected in studies using molecular karyotyping (SNP array). Despite this type of variation being able to provide meaningful data on the parents' kinship, uniparental disomy and chromosome rearrangements, LCSH are rarely considered as a possible epigenetic cause of neurodevelopmental disorders. Despite their direct relationship to imprinting, LCSH in imprinted loci have not been considered in terms of pathogenicity. The present work is aimed at studying LCSH in chromosomal regions containing imprinted genes previously associated with disease in children with idiopathic intellectual disability, autism, congenital malformations and/or epilepsy.
MATERIAL AND METHODS: Five hundred and four patients with autism spectrum disorders and intellectual disability were examined**.**
RESULTS: LCSH affecting imprinted loci associated with various diseases were identified in 40 (7.9%) individuals. Chromosomal region 7q21.3 was affected in twenty three cases, 15q11.2 in twelve, 11p15.5 in five, 7q32.2 in four. Four patients had 2 LCSH affecting imprinted loci. Besides one LCSH in 7q31.33q32.3 (~4 Mbp) region, all LCSH were 1-1.6 Mbp. Clinically, these cases resembled the corresponding imprinting diseases (e.g. Silver-Russell, Beckwith-Wiedemann, Prader-Willi, Angelman syndromes). Parental kinship was identified in 8 cases (1.59%), which were not affected by LCSH at imprinted loci.
CONCLUSION: The present study shows that LCSH affecting chromosomal regions 7q21.3, 7q32.2, 11p15.5 and 15p11.2 occur in about 7.9% of children with intellectual disability, autism, congenital malformations and/or epilepsy. Consequently, this type of epigenetic mutations is obviously common in a group of children with neurodevelopmental disorders. LCSH less than 2.5-10 Mbp are usually ignored in molecular karyotyping (SNP array) studies and, therefore, an important epigenetic cause of intellectual disability, autism or epilepsy with high probability remains without attention.
KEYWORDS: autism; bioinformatics; congenital malformations; epigenetics; epilepsy; intellectual disability; stretches of homozygosity
PMID:31317896 DOI:10.17116/jnevro201911905191

Ge MM, Gao YY, Wu BB, Yan K, Qin Q, Wang H, Zhou W, Yang L Relationship between phenotype and genotype of 102 Chinese newborns with Prader-Willi syndrome. Mol Biol Rep. 2019 Jul 3.. [Epub ahead of print]

Abstract High rates of misdiagnosis and delayed intervention in neonatal PWS are leading to poor prognoses. To determine the clinical and image characteristics of newborns with Prader-Willi syndrome (PWS). A total of 102 cases of newborns definitively diagnosed with PWS at the Children's Hospital of Fudan University from 02/2014 to 12/2017 were retrospectively analyzed. We analyzed the modulated voxel-based morphology (VBM) of gray matter in PWS by T2 weighted imaging. Of 102 cases, 75 (73.5%) have paternal deletion of 15q11.2-q13, whereas 27 (26.5%) have maternal uniparental disomy (UPD). Of the 75 deletion cases, 75 (100%) week crying, 71 (94.7%) hypotonia, 70 (93.3%) poor feeding, 46 (61.3%) hypopigmentation, 43 (57.3%) male cryptorchidism, 10 (13.3%) female labia minora, 48 (64%) characteristic facial features. Of 27 UPD cases, 27 (100%) week crying and hypotonia, 25 (92.6%) hypophagia, 20 (74.1%) male cryptorchidism, 1 (3.7%) female labia minora, 19 (70.4%) characteristic facial features, 12 (44.4%) hypopigmentation. The modulated VBM analysis shows that the middle frontal gyrus, orbitofrontal cortex (middle), and inferior frontal gyrus

are the most variable brain regions that determine the endo-phenotype difference between the two genotypes. Hypotonia, hypophagia, and maldevelopment of sexual organs are general characteristics of newborns with PWS in Chinese population. In UPD cases, the proportions of premature newborns, elderly parturient women and congenital malformations were higher than for paternal deletion cases. The differences in the gray matter volume of these three regions between the two genotypes may explain the differences in maladaptive behaviors and emotions.
KEYWORDS: Clinical manifestation; Genotype; Image; Newborn; Prader–Willi syndrome
PMID:31270759 DOI:10.1007/s11033-019-04916-2

Chen W, Xu D, Ma C, Zhang C, Li J, Zhang W, Zhao G, Li S. The molecular structure and imprinting status of the IPW (imprinted gene in the Prader-Willi syndrome region) gene in cattle. Anim Genet. 2019 Jul 3. [Epub ahead of print]
Abstract IPW (imprinted gene in the Prader-Willi syndrome region), a long non-coding RNA, is a paternally expressed gene in the PWS/AS imprinted domain on human chromosome 15 and mouse chromosome 7. Disruption of the PWS/AS region is associated with three neurogenic disorders in humans. In this study, we identified the bovine homolog of the IPW gene; multiple transcripts obtained by RT-PCR and RACE showed a complex and tissue-specific expression pattern of IPW in the brain, heart, kidney, liver, lung, spleen and skeletal muscle. An informative single nucleotide polymorphism (rs133341090) in the long exon H was identified by sequencing the genomic DNA, and mono-allelic expression of IPW was confirmed by sequencing the cDNAs of heterozygous individuals, indicating that IPW may be imprinted in cattle. The protein-coding potential of IPW transcripts was assessed using coding potential calculator (cpc) software, which showed a negative score. In addition, sequencing analysis also indicated multiple small open reading frames in the bovine IPW transcript, but none of the ATGs was consistent with Kozak consensus. Taken together, the IPW transcripts are most likely long non-coding RNAs.
KEYWORDS: Imprinted gene in the Prader-Willi syndrome region; bovine; imprinted; lncRNA; splice variants
PMID:31268171 DOI:10.1111/age.12815

Endocrine including GH

Yang A, Choi JH, Sohn YB, Eom Y, Lee J, Yoo HW, Jin DK. Effects of recombinant human growth hormone treatment on growth, body composition, and safety in infants or toddlers with Prader-Willi syndrome: a randomized, active-controlled trial. Orphanet J Rare Dis. 2019 Sep 11;14(1):216.
Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare complex genetic disorder and is characterized by short stature, muscular hypotonia, abnormal body composition, psychomotor retardation, and hyperphagia. Recombinant human growth hormone (rhGH) treatment improves the symptoms in children with PWS, and early treatment results in more favorable outcomes. However, systematic studies in infants and toddlers under 2 years of age are lacking. This multicenter, randomized, active-controlled, parallel-group, open-label, Phase III study aimed to evaluate the safety of rhGH (Eutropin, LG Chem, Ltd.) and its efficacy on growth, body composition, and motor and cognitive development in infants and toddlers with PWS compared with a comparator treatment (Genotropin, Pfizer, Inc.). Eligible Korean infants or toddlers with PWS were randomly assigned to receive Eutropin or comparator (both 0.24 mg/kg/week, 6 times/week) for 1 year. Height standard deviation score (SDS), body composition, and motor and cognitive development were measured. RESULTS: Thirty-four subjects (less than 24 months old) were randomized into either the Eutropin (N = 17) group or the comparator (N = 17) group. After 52 weeks of rhGH treatment, height SDS and lean body mass increased significantly from baseline in both groups: the mean height SDS change (SD) was 0.75 (0.59) in the Eutropin group and 0.95 (0.66) in the comparator group, and the mean

lean body mass change (SD) was 2377.79 (536.25) g in the Eutropin group and 2607.10 (641.36) g in the comparator group. In addition, percent body fat decreased significantly: the mean (SD) change from baseline was - 8.12% (9.86%) in the Eutropin group and - 7.48% (10.26%) in the comparator group. Motor and cognitive developments were also improved in both groups after the 1-year treatment. The incidence of adverse events was similar between the groups.
CONCLUSIONS: rhGH treatment for 52 weeks in infants and toddlers with PWS improved growth, body composition, and motor and cognitive development, and efficacy and safety outcomes of Eutropin were comparable to those of Genotropin. Hence, Eutropin is expected to provide safe and clinically meaningful improvements in pediatric patients with PWS.
TRIAL REGISTRATION: The study was registered at ClinicalTrials.gov (identifier: NCT02204163) on July 30, 2014. URL: https://clinicaltrials.gov/ct2/show/NCT02204163?term=NCT02204163&rank=1.
KEYWORDS: Body composition; Growth hormone therapy; Infants and toddlers; Prader-Willi syndrome; Psychomotor development
PMID:31511031 PMCID:PMC6739953 DOI:10.1186/s13023-019-1195-1

Palmieri VV, Lonero A, Bocchini S, Cassano G, Convertino A, Corica D, Crinò A, Fattorusso V, Ferraris S, Fintini D, Franzese A, Grugni G, Iughetti L, Lia R, Macchi F, Madeo SF, Matarazzo P, Nosetti L, Osimani S, Pajno R, Patti G, Pellegrin MC, Perri A, Ragusa L, Rutigliano I, Sacco M, Salvatoni A, Scarano E, Stagi S, Tornese G, Trifirò G, Wasniewska M, Fischetto R, Giordano P, Licenziati MR, Delvecchio M; Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Uniparental disomy and pretreatment IGF-1 may predict elevated IGF-1 levels in Prader-Willi patients on GH treatment. Growth Horm IGF Res. 2019 Aug 28;48-49:9-15.. [Epub ahead of print]

Abstract Pediatric patients with Prader-Willi syndrome (PWS) can be treated with recombinant human GH (rhGH). These patients are highly sensitive to rhGH and the standard doses suggested by the international guidelines often result in IGF-1 above the normal range. We aimed to evaluate 1 the proper rhGH dose to optimize auxological outcomes and to avoid potential overtreatment, and 2 which patients are more sensitive to rhGH. In this multicenter real-life study, we recruited 215 patients with PWS older than 1 year, on rhGH at least for 6 months, from Italian Centers for PWS care. We collected auxological parameters, rhGH dose, IGF-1 at recruitment and (when available) at start of treatment. The rhGH dose was 4.3 (0.7/8.4) mg/m^2/week. At recruitment, IGF-1 was normal in 72.1% and elevated in 27.9% of the patients. In the group of 115 patients with IGF-1 available at start of rhGH, normal pretreatment IGF-1 and uniparental disomy were associated with elevated IGF-1 during the therapy. No difference in height and growth velocity was found between patients treated with the highest and the lowest range dose. The rhGH dose prescribed in Italy seems lower than the recommended one. Normal pretreatment IGF-1 and uniparental disomy are risk factors for elevated IGF-1. The latter seems to be associated with higher sensitivity to GH. In case of these risk factors, we recommend a more accurate titration of the dose to avoid overtreatment and its potential side effects.
KEYWORDS: Adverse effects; Growth hormone therapy; IGF-1; Prader-Willi syndrome; Uniparental disomy
PMID:31487604 DOI:10.1016/j.ghir.2019.08.003

Laumonerie P, Tibbo ME, Ibnoulkhatib A, Kerezoudis P, Diene G, Thevenin Lemoine C, Accadbled F, Sales de Gauzy J. Evolution of Hip Dysplasia in Pediatric Patients With Prader-Willi Syndrome Treated With Growth Hormone Early in Development. J Pediatr Orthop. 2019 Aug 30. [Epub ahead of print]

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by obesity, hypotonia, feeding difficulties, obesity, musculoskeletal manifestations including scoliosis, and hip dysplasia (HD). The aim of this study was to characterize the clinical and radiographic evolution of HD in the pediatric PWS population.
METHODS: The authors performed a retrospective cohort study of 72 patients (147 anteroposterior pelvic radiographs) between January 2004 and December 2016. Center-edge angle (CEA) of Wiberg, acetabular index (AI), and neck-shaft angle (NSA) were measures in all hips. The relationship between radiographic and demographic parameters of age, sex, and body mass index z-score (BMIzs) were assessed.
RESULTS: A total of 274 radiographic measurements were performed and analyzed in 72 patients. The mean CEA, AI, and NSA were 21.8±7.1 degrees (range, 5 to 35 degrees), 16.7±7 degrees (range, 5 to 45 degrees), and 142±8.5 degrees (range, 128 to 165 degrees), respectively. HD was diagnosed in 79 (29%) hip radiographs and varied significantly between the age groups ($P<0.01$). A statistically significant association was identified between age and CEA [β coef, 0.80; 95% confidence interval (CI), 0.6-1; $P<0.01$], AI (β coef, -0.90; 95% CI, -1.1 to -0.7; $P<0.01$), and NSA (β coef, -1.11; 95% CI, -1.4 to -0.9; $P<0.01$) angles. Sex and BMIzs were not identified as independent predictors of radiographic hip angles ($P>0.1$).
CONCLUSIONS: The present study demonstrated favorable evolution of hip radiographic parameters in the PWS population treated with growth hormone early in development. This finding should prompt orthopedists to consider observation alone in the management algorithm for HD in patients with PWS.
LEVELS OF EVIDENCE: Level III-a retrospective comparative study.
PMID:31479030 DOI:10.1097/BPO.0000000000001443

Braxton TM, Sarpong DE, Dovey JL, Guillou A, Evans B, Castellano JM, Keenan BE, Baraghithy S, Evans SL, Tena-Sempere M, Mollard P, Tam J, Wells T. Thermoneutrality improves skeletal impairment in adult Prader-Willi syndrome mice. J Endocrinol. 2019 Aug 1. pii: JOE-19-0279.R1.. [Epub ahead of print

Abstract Human Prader-Willi syndrome (PWS) is characterised by impairments of multiple systems including the growth hormone (GH) axis and skeletal growth. To address our lack of knowledge of the influence of PWS on skeletal integrity in mice, we have characterised the endocrine and skeletal phenotype of the PWS-ICdel mouse model for "full" PWS and determined the impact of thermoneutrality. Tibial length, epiphyseal plate width and marrow adiposity were reduced by 6%, 18% and 79% in male PWS-ICdel mice, with osteoclast density being unaffected. Similar reductions in femoral length accompanied a 32% reduction in mid-diaphyseal cortical diameter. Distal femoral Tb.N was reduced by 62%, with individual trabeculae being less plate-like and the lattice being more fragmented (Tb.Pf increased by 63%). Cortical strength (Ultimate moment) was reduced by 26% as a result of reductions in calcified tissue strength and the geometric contribution. GH and prolactin contents in PWS-ICdel pituitaries were reduced in proportion to their smaller pituitary size, with circulating IGF-1 concentration reduced by 37-47%. Conversely, while pituitary LH content was halved, circulating gonadotropin concentrations were unaffected. Although longitudinal growth, marrow adiposity and femoral geometry were unaffected by thermoneutrality, strengthened calcified tissue reversed weakened cortex of PWS-ICdel femora. While underactivity of the GH-axis may be due to loss of Snord116 expression and impaired limb bone geometry and strength due to loss of Magel2 expression, comprehensive analysis of skeletal integrity in the single gene deletion models is required. Our data imply that thermoneutrality may ameliorate the elevated fracture risk associated with PWS.
PMID:31454785 DOI:10.1530/JOE-19-0279

Donze SH, Hokken-Koelega ACS. Reply to Commentary on 'Prevalence of growth hormone (GH) deficiency in previously GH treated young adults with Prader-Willi syndrome'. Clin Endocrinol (Oxf). 2019 Jul 23.. [Epub ahead of print]

Abstract Data sharing is not applicable to this article as no new data were created or analyzed in this study. We would like to thank the authors for their commentary as it gives us the opportunity to repeat our conclusion that adults with PWS should be treated with growth hormone (GH), regardless of GH stimulation test results. Our findings show that conventional testing for adult GHD is not reliable in adults with Prader-Willi syndrome (PWS).

PMID:31335978 DOI:10.1111/cen.14066

Deng L, Wang R, Li H, Zhang C, Zhao L, Zhang M. miRNA-Gene Regulatory Network in Gnotobiotic Mice Stimulated by Dysbiotic Gut Microbiota Transplanted From a Genetically Obese Child. Front Microbiol. 2019 Jul 5;10:1517.. eCollection 2019.

Abstract Gut microbiota (GM) dysbiosis has been considered a pathogenic origin of many chronic diseases. In our previous trial, a shift in GM structure caused by a complex fiber-rich diet was associated with the health improvement of obese Prader-Willi syndrome (PWS) children. The pre- and post-intervention GMs (pre- and post-group, respectively) from one child were then transplanted into gnotobiotic mice, which resulted in significantly different physiological phenotypes, each of which was similar to the phenotype of the corresponding GM donor. This study was designed to investigate the miRNA-gene regulatory networks involved in causing these phenotypic differences. Using the post-group as a reference, we systematically identified and annotated the differentially expressed (DE) miRNAs and genes in the colon and liver of the pre-group in the second and fourth weeks after GM inoculation. Most of the significantly enriched GO terms and KEGG pathways were observed in the liver and were in the second week after GM transplantation. We screened 23 key genes along with their 73 miRNA regulators relevant to the host phenotype changes and constructed a network. The network contained 92 miRNA-gene regulation relationships, 51 of which were positive, and 41 of which were negative. Both the colon and liver had upregulated pro-inflammatory genes, and genes involved in fatty acid oxidation, lipolysis, and plasma cholesterol clearance were downregulated in only the liver. These changes were consistent with lipid and cholesterol accumulation in the host and with a high inflammation level. In addition, the colon showed an impacted glucagon-like peptide 1 (GLP-1) signaling pathway, while the liver displayed decreased insulin receptor signaling pathway activity. These molecular changes were mainly found in the second week, 2 weeks before changes in body fat occurred. This time lag indicated that GM dysbiosis might initially induce cholesterol and lipid metabolism-related miRNA and gene expression disorder and then lead to lipid accumulation and obesity development, which implicates a causative role of GM dysbiosis in obesity development rather than a result of obesity. This study provides fundamental molecular information that elucidates how dysbiotic GM increases host inflammation and disturbs host lipid and glucose metabolism.

KEYWORDS: gene expression; gnotobiotic mice; gut microbiota; inflammation; lipid and glucose metabolism; miRNA; regulatory network

PMID:31333621 PMCID:PMC6624655 DOI:10.3389/fmicb.2019.01517

.

Canning DA. Re: Orchidopexy in Children with Prader-Willi Syndrome: Results of a Long-Term Follow-up Study. J Urol. 2019 Jul 9:10109701JU000057701264888f4.. [Epub ahead of print]

PMID:31287359 DOI:10.1097/01.JU.0000577012.64888.f4

Corripio R, Tubau C, Calvo L, Brun C, Capdevila N, Larramona H, Gabau E. Safety and effectiveness of growth hormone therapy in infants with Prader-Willi syndrome younger than 2 years: a prospective study. J Pediatr Endocrinol Metab. 2019 Jul 4. pii: /j/jpem.ahead-of-print/jpem-2018-0539/jpem-2018-0539.xml. . [Epub ahead of print]

Abstract BACKGROUND There is little evidence of the effects of early treatment with growth hormone (GH) in infants with Prader-Willi syndrome (PWS). A prospective study was conducted to assess the safety of GH therapy in infants younger than 2 years of age with PWS.
METHODS A total of 14 patients with PWS started treatment with GH under the age of 2 years and were followed over a 2-year period. A deletion of chromosome 15 was present in nine infants (64.3%) and maternal uniparental disomy 15 in five infants (35.7%). The median age at start of GH treatment was 9.6 months (interquartile range [IQR] 9.0-18.3 months). Changes in height standard deviation score (SDS), body mass index (BMI) SDS and subcapsular and tricipital skinfolds in the follow-up period were evaluated with a mixed-model regression analysis using the Package R.
RESULTS There were no fatal adverse events. A significant decrease ($p < 0.001$) in tricipital and subcapsular skinfold thickness, with an upward trend of height SDS and a downward trend of BMI SDS, was observed. Infants who started GH before 15 months of age started walking at a median of 18.0 [17.0-19.5] months vs. 36.6 [36.3-37.8] months for those who began treatment with GH after 15 months of age ($p = 0.024$).
CONCLUSIONS GH treatment in infants with PWS less than 2 years of age is safe and improved body composition. Infants who received GH before the age of 15 months started to walk earlier.
KEYWORDS: Prader-Willi syndrome; body composition; growth hormone
PMID:31271556 DOI:10.1515/jpem-2018-0539

Sensory and physical

Liu SY, Wong SK, Lam CC, Ng EK. Bariatric surgery for Prader-Willi syndrome was ineffective in producing sustainable weight loss: Long term results for up to 10 years. Pediatr Obes. 2019 Sep 12. [Epub ahead of print]

Abstract BACKGROUND: Obesity control in Prader-Willi syndrome (PWS) is notoriously difficult. The role of bariatric surgery in PWS remains controversial as long-term data are lacking.
OBJECTIVES: To evaluate the 10-year outcomes of bariatric surgery in PWS.
METHODS: This was a prospective observational study on PWS patients who received bariatric surgery and multidisciplinary follow-up programmes for obesity control. Outcomes on weight reduction and comorbidity resolution were evaluated.
RESULTS: Between 2008 and 2013, five PWS patients (two males, mean age 19.2 ± 3.0 years) with body mass index of 47.3 ± 6.9 kg m^{-2} received sleeve gastrectomy (n = 2), one anastomosis gastric bypass (n = 2), and Roux-en-Y gastric bypass (n = 1) after failing all non-operative weight loss programmes. The median follow-up was 8.4 ± 2.2 years. The best mean percentage of total weight loss (%TWL) was achieved at 2 years (24.7%). %TWL dropped to 23.3% at 3 years, 11.9% at 5 years, 4.1% at 8 years, and 0% at 10 years. Each patient had at least three comorbidities preoperatively, but none of them had resolution of any one of the comorbidities at the last follow-up.
CONCLUSIONS: Bariatric surgery could not produce sustainable long-term weight loss or comorbidity resolution in PWS. This study suggests that bariatric surgery cannot be recommended to PWS patients as a standard treatment.
KEYWORDS: Prader-Willi syndrome; bariatric surgery; morbid; obesity, paediatric obesity; weight loss
PMID:31515962 DOI:10.1111/ijpo.12575

Demir K, Konakçı E, Özkaya G, Kasap Demir B, Özen S, Aydın M, Darendeliler F. New Features for Child Metrics: Further Growth References and Blood Pressure Calculations J Clin Res Pediatr Endocrinol. 2019 Sep 2.. [Epub ahead of print]

Abstract Many new features have recently been incorporated to ÇEDD Çözüm / Child Metrics, an online and freely accessible scientific toolset. Various auxological assessments can now be made with

data of children with genetic diseases (Prader Willi syndrome, Noonan syndrome, Turner syndrome, Down syndrome, and Achondroplasia) and preterm and term newborns. More detailed reports for height, weight, and body mass index (BMI) data of a given child are now available. Last but not least, office and 24-hour ambulatory blood pressure values can be analyzed according to normative data.
KEYWORDS: Application; mobile; calculator; short stature; growth chart; hypertension; guideline; AAP
PMID:31475511 DOI:10.4274/jcrpe.galenos.2019.2019.0127

Laumonerie P, Tibbo ME, Ibnoulkhatib A, Kerezoudis P, Diene G, Thevenin Lemoine C, Accadbled F, Sales de Gauzy J. Evolution of Hip Dysplasia in Pediatric Patients With Prader-Willi Syndrome Treated With Growth Hormone Early in Development. J Pediatr Orthop. 2019 Aug 30.. [Epub ahead of print]

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by obesity, hypotonia, feeding difficulties, obesity, musculoskeletal manifestations including scoliosis, and hip dysplasia (HD). The aim of this study was to characterize the clinical and radiographic evolution of HD in the pediatric PWS population.
METHODS: The authors performed a retrospective cohort study of 72 patients (147 anteroposterior pelvic radiographs) between January 2004 and December 2016. Center-edge angle (CEA) of Wiberg, acetabular index (AI), and neck-shaft angle (NSA) were measures in all hips. The relationship between radiographic and demographic parameters of age, sex, and body mass index z-score (BMIzs) were assessed.
RESULTS: A total of 274 radiographic measurements were performed and analyzed in 72 patients. The mean CEA, AI, and NSA were 21.8±7.1 degrees (range, 5 to 35 degrees), 16.7±7 degrees (range, 5 to 45 degrees), and 142±8.5 degrees (range, 128 to 165 degrees), respectively. HD was diagnosed in 79 (29%) hip radiographs and varied significantly between the age groups ($P<0.01$). A statistically significant association was identified between age and CEA [β coef, 0.80; 95% confidence interval (CI), 0.6-1; $P<0.01$], AI (β coef, -0.90; 95% CI, -1.1 to -0.7; $P<0.01$), and NSA (β coef, -1.11; 95% CI, -1.4 to -0.9; $P<0.01$) angles. Sex and BMIzs were not identified as independent predictors of radiographic hip angles ($P>0.1$).
CONCLUSIONS: The present study demonstrated favorable evolution of hip radiographic parameters in the PWS population treated with growth hormone early in development. This finding should prompt orthopedists to consider observation alone in the management algorithm for HD in patients with PWS.
LEVELS OF EVIDENCE: Level III-a retrospective comparative study.
PMID:31479030 DOI:10.1097/BPO.0000000000001443

Lima FCB, do Nascimento Junior EB, Teixeira SS, Coelho FM, Oliveira GDP. Thinking outside the box: cataplexy without narcolepsy. Sleep Med. 2019 Mar 20. pii: S1389-9457(19)30068-1.. [Epub ahead of print]

Abstract Cataplexy is a transient loss of muscle tone that can be triggered by emotions such as laughter, excitement or fear. Other causes of cataplexy include Niemann-Pick type C Disease, Angelman Syndrome, Norrie Disease, Prader-Willi Syndrome. In addition, cataplexy can be a side effect of several drugs (eg, lamotrigine, clozapine, and gamma-hydroxybutyrate). Yet, the most prevalent causes of cataplexy without narcolepsy are rare genetic diseases; which explains why cataplexy is classically linked to narcolepsy. Therefore, it is essential disconnecting cataplexy from narcolepsy especially in pediatric population and after use of a few medications. In this review, we described few conditions of cataplexy not related to narcolepsy. We performed a review of literature (MEDLINE and EMBASE database), without limited date or publication restrictions.
KEYWORDS: Angelman Syndrome; Cataplexy; Narcolepsy; Niemann-Pick type C Disease; Norrie Disease; Prader-Willi Syndrome
PMID:31427075 DOI:10.1016/j.sleep.2019.03.006

Oore J, Connell B, Yaszay B, Samdani A, Hilaire TS, Flynn T, El-Hawary R; Children's Spine Study Group; Growing Spine Study Group. Growth Friendly Surgery and Serial Cast Correction in the Treatment of Early-onset Scoliosis for Patients With Prader-Willi Syndrome. J Pediatr Orthop. 2019 Sep;39(8):e597-e601.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) patients can present with scoliosis which can be treated with serial cast correction (SCC) or with growth friendly surgery (GFS). This study's purpose was to describe the results of SCC as well as GFS for PWS patients with early-onset scoliosis (EOS).

METHODS: PWS patients were identified from 2 international multicenter EOS databases. Scoliosis, kyphosis, spine height (T1-S1), right/left hemithoracic heights/widths (RHTH, LHTH, RHTW, LHTW) were measured pretreatment, postoperation, and at 2-year follow-up. Complications were recorded.

RESULTS: Overall, 23 patients with 2-year follow-up were identified. Pretreatment; patients treated with SCC (n=10) had mean age of 1.8±0.6 years; body mass index (BMI), 16±1.5 kg/m; scoliosis, 45±18 degrees; kyphosis, 56±9 degrees; T1-S1, 22.4±2.4 cm; RHTH, 8.0±2.0 cm; LHTH, 8.5±1.7 cm; RHTW, 6.6±1.3 cm; and LHTW, 8.0±1.0 cm. Patients treated with GFS (n=13) had mean age of 5.8±2.6 years; BMI, 21±5.4 kg/m; scoliosis, 76±14 degrees; kyphosis, 59±25 degrees; T1-S1, 24.1±3.6 cm; RHTH, 10.0±1.6 cm; LHTH, 10.6±1.6 cm; RHTW, 9.4±2.5 cm; and LHTW, 8.1±2.8 cm. At 2-year follow-up, patients treated with SCC had mean scoliosis 37±11 degrees (18% correction, P=0.06); kyphosis, 42±6 degrees (NS); T1-S1, 26.4±2.1 cm (P<0.01); RHTH, 9.0±1.1 cm (13%; P=0.30); LHTH, 10.0±1.5 cm (18%, P<0.01); RHTW, 7.4±1.1 cm (12%, P<0.01); and LHTW, 8.0±1.0 cm (0%, P=0.34). At 2-year follow-up, patients treated with GFS had mean scoliosis 42±13 degrees (45% correction, P<0.000001); kyphosis, 53±13 degrees (10%, P=0.19); T1-S1, 31.5±5.4 cm (P<0.00001); RHTH, 12.0±2.4 cm (20%; P<0.01); LHTH, 12.0±1.7 cm (13%; P<0.01); RHTW, 9.8±1.3 cm (4%; P=0.27); and LHTW, 7.9±2.3 cm (3%;P=0.11). As an entire group, patients with a BMI>17 kg/m² had more device-related than disease-related complications (P=0.09). Patients treated with SCC had 0.9 complications per patient. Patients treated with GFS had 2.2 complications per patient [≤5 y more often had ≥2 complications (P=0.05)].

CONCLUSIONS: At 2-year follow-up, SCC and GFS were both effective in treating EOS in PWS patients. Patients treated with SCC had significant improvements in spine height and LHTH. Patients treated with GFS had significant improvements in scoliosis magnitude, spine height, RHTH, and LHTH.

LEVEL OF EVIDENCE: Level IV-therapeutic study.

PMID:31393296 DOI:10.1097/BPO.0000000000001123

Salvatoni A, Moretti A, Grugni G, Agosti M, Azzolini S, Bonaita V, Cianci P, Corica D, Crinò A, Delvecchio M, Ferraris S, Greggio NA, Iughetti L, Licenziati MR, Madeo SF, Nosetti L[1]Pajno R, Rutigliano I, Sacco M, Salvatore S, Scarano E, Trifirò G, Wasniewska M. Anthropometric characteristics of newborns with Prader-Willi syndrome. Am J Med Genet A. 2019 Jul 30.. [Epub ahead of print]

Abstract This is a retrospective multicenter nationwide Italian study collecting neonatal anthropometric data of Caucasian subjects with Prader-Willi syndrome (PWS) born from 1988 to 2018. The aim of the study is to provide percentile charts for weight and length of singletons with PWS born between 36 and 42 gestational weeks. We collected the birth weight and birth length of 252 male and 244 female singleton live born infants with both parents of Italian origin and PWS genetically confirmed. Percentile smoothed curves of birth weight and length for gestational age were built through Cole's lambda, mu, sigma method. The data were compared to normal Italian standards. Newborns with PWS showed a lower mean birth weight, by 1/2 kg, and a shorter mean birth length, by 1 cm, than healthy neonates. Females with a 15q11-13 deletion were shorter than those with maternal uniparental maternal disomy of chromosome 15 ($p < .0001$). The present growth curves may be useful as further traits in supporting a suspicion of PWS in a newborn. Because impaired prenatal growth increases risk of health problems later in life, having neonatal anthropometric standards could be helpful to evaluate possible correlations between the presence or absence of small gestational age and some clinical and metabolic aspects of PWS.

KEYWORDS: Prader-Willi; growth; newborn; percentiles
PMID:31361394 DOI:10.1002/ajmg.a.61304

Manzardo AM, Heinemann J, McManus B, Loker C, Loker J, Butler MG. Venous Thromboembolism in Prader-Willi Syndrome: A Questionnaire Survey. Genes (Basel). 2019 Jul 19;10(7). pii: E550..

Abstract Prader-Willi Syndrome Association (USA) monitors the ongoing health and welfare of individuals with Prader-Willi syndrome (PWS) through active communication with members by membership surveys and data registries. Thromboembolism and blood clots have emerged in clinical studies as significant risk factors for injury and death in PWS. A 66-item questionnaire was developed by a panel of PWS medical and scientific experts, with input from Prader-Willi Syndrome Association (USA) leadership, so as to probe their membership on the frequency, risk, and protective factors for venous thromboembolism, pulmonary embolism, and related findings. The characteristics of those with and without a reported history of blood clots and related health factors were tabulated and analyzed. Responses were obtained for 1067 individuals with PWS (554 females and 513 males), and 38 (23 females and 15 males) had a history of blood clots. The individuals with clots did not differ by gender, but were significantly older 32.8 ± 15 years vs 20.4 ± 13 years, and were more likely to have a reported history of obesity (76%), edema (59%), hypertension (24%), vasculitis (33%), and family history of blood clots (33%) than those without clots. Growth hormone treatment was more common in individuals without clots. The risk factors for thromboembolism in PWS overlap those commonly observed for the general population.

KEYWORDS: Prader–Willi syndrome; blood clots; risk factors; thromboembolism; vasculitis
PMID:31331040 DOI:10.3390/genes10070550

Bantim YCV, Kussaba ST, de Carvalho GP, Garcia-Junior IR, Roman-Torres CVG. Oral health in patients with Prader-Willi syndrome: current perspectives. Clin Cosmet Investig Dent. 2019 Jul 4;11:163-170.. eCollection 2019.

Abstract Prader-Willi syndrome (PWS) is a rare complex multisystem disorder and presents several aspects related to dentistry. The purpose of this review is to present current perspectives about oral health in patients with PWS. Delay development, hyperphagia, foamy and highly viscous saliva raise the risk of caries and contribute to tooth wear. Cariogenic foods uncontrolled consumption allows to obesity and dental problems progress worsening systemic disorders. These factors can be controlled. The success in follow-ups with caries free and oral health controlled demonstrate the importance of multidisciplinary team intervention corroborated by support at home from birth to adulthood. Thereby, current perspective on the disease is that there is possibility of proper maintenance of oral health in PWS patients. Guided care interferes positively with the overall well-being and quality of life of the individual with PWS and their family. A multidisciplinary team with a focus on teaching patients and family members will help minimize eventual problems.

KEYWORDS: Prader-Willi syndrome; oral health; patient care management
PMID:31308759 PMCID:PMC6613606 DOI:10.2147/CCIDE.S183981

Behaviour

Kimonis V, Surampalli A, Wencel M, Gold JA, Cowen NM. A randomized pilot efficacy and safety trial of diazoxide choline controlled-release in patients with Prader-Willi syndrome PLoS One. 2019 Sep 23;14(9):e0221615.. eCollection 2019.

Abstract INTRODUCTION: Prader-Willi syndrome (PWS) is a complex genetic condition characterized by hyperphagia, hypotonia, low muscle mass, excess body fat, developmental delays, intellectual disability, behavioral problems, and growth hormone deficiency. This study evaluated the safety and efficacy of orally administered Diazoxide Choline Controlled-Release Tablets (DCCR) in subjects with PWS.

METHOD: This was a single-center, Phase II study and included a 10-week Open-Label Treatment Period during which subjects were dose escalated, followed by a 4-week Double-Blind, Placebo-Controlled Treatment Period.

RESULTS: Five female and eight male overweight or obese, adolescent and adult subjects with genetically-confirmed PWS with an average age of 15.5±2.9 years were enrolled in the study. There was a statistically significant reduction in hyperphagia at the end of the Open-Label Treatment Period (-4.32, n = 11, p = 0.006). The onset of effect on hyperphagia was rapid and greater reductions in hyperphagia were seen in subjects with moderate to severe Baseline hyperphagia (-5.50, n = 6, p = 0.03), in subjects treated with the highest dose (-6.25, n = 4, p = 0.08), and in subjects with moderate to severe Baseline hyperphagia treated with the highest dose (-7.83, n = 3, p = 0.09). DCCR treatment resulted in a reduction in the number of subjects displaying aggressive behaviors (-57.1%, n = 10, p = 0.01), clinically-relevant reductions in fat mass (-1.58 kg, n = 11, p = 0.02) and increases in lean body mass (2.26 kg, n = 11, p = 0.003). There was a corresponding decrease in waist circumference, and trends for improvements in lipids and insulin resistance. The most common adverse events were peripheral edema and transient increases in glucose. Many of the adverse events were common medical complications of PWS and diazoxide.

CONCLUSION: DCCR treatment appears to address various unmet needs associated with PWS, including hyperphagia and aggressive behaviors in this proof-of-concept study. If the results were replicated in a larger scale study, DCCR may be a preferred therapeutic option for patients with PWS.

PMID:31545799 DOI:10.1371/journal.pone.0221615

Kato E, Kimura M, Okuda T, Toyoda M, Fukagawa M. Behavior Modification Maintenance with Long-Term Blood Glucose and Weight Management in Prader-Willi Syndrome Complicated with Diabetes: Team Management Approach Combined with Pharmacological Treatment. Case Rep Med. 2019 Jul 8;2019:6129019.. eCollection 2019.

Abstract The patient was a 40-year-old woman, who had been diagnosed with Prader-Willi syndrome (PWS) at 1 year of age and type 2 diabetes at 27 years of age. At 34 years of age, she was hospitalized to start insulin therapy and receive guidance on treatment. During the next 6 months and through regular once-monthly outpatient clinic visits, the blood glucose level was relatively stabilized although body weight gradually increased. Two years following discharge, the blood glucose level became unstable, and she was hospitalized again to receive guidance on treatment. A team medicine-based approach was established upon hospitalization. The basic treatment was unchanged (insulin, diet, and exercise). The approach taken by the team included understanding the characteristics of PWS by all team members, clear definition of treatment goals, positive evaluation of the patient, and maintenance of the patient's motivation for treatment. Anxiety and stress related to mother's illness dampened motivation and adherence to treatment, but the addition of appropriate pharmacological treatment helped in rapid recovery of motivation to adhere to the treatment protocol. At 3 years after discharge, HbA1c is maintained at around 6%, and body weight continues to fall. Our protocol of the combination of a team medicine approach with appropriately timed pharmacological intervention could probably be applied to not only type 2 diabetes in PWS but also the management of patients with poorly controlled type 2 diabetes.

PMID:31360171 PMCID:PMC6644266 DOI:10.1155/2019/6129019

Devine DP. Animal Models of Self-Injurious Behavior: An Update. Methods Mol Biol. 2019;2011:41-60.

Abstract Although self-injurious behavior is a common comorbid behavior problem among individuals with neurodevelopmental disorders, little is known about its etiology and underlying neurobiology. Interestingly, it shows up in various forms across patient groups with distinct genetic errors and diagnostic categories. This suggests that there may be shared neuropathology that confers vulnerability in these disparate groups. Convergent evidence from clinical pharmacotherapy, brain imaging studies, postmortem neurochemical analyses, and animal models indicates that dopaminergic insufficiency is a key contributing factor. This chapter provides an overview of studies in which animal models have been used to investigate the biochemical basis of self-injury and highlights the convergence in findings between these models and expression of self-injury in humans.

KEYWORDS: Animal model; Dopamine; Lesch-Nyhan syndrome; Prader-Willi syndrome; Self-injurious behavior; Striatum

PMID:31273692 DOI:10.1007/978-1-4939-9554-7_3

Cognition and mental health

Dimitropoulos A, Zyga O, Russ SW. Early Social Cognitive Ability in Preschoolers with Prader-Willi Syndrome and Autism Spectrum Disorder. J Autism Dev Disord. 2019 Aug 6.. [Epub ahead of print]

Abstract Children with Prader-Willi syndrome (PWS) and autism spectrum disorder (ASD) present with challenges in social cognitive ability, Research comparing PWS to ASD is important given the implication of 15q11-q13 region in the biology of autism. However, recent findings question the accuracy of relying solely on parent report in behavioral characterization. Thus, this study examined social cognition in an observable pretend play task and by parent report in 50 preschool children (ages 3-5) with PWS, by subtype, compared to ASD. Behaviorally, the paternal deletion subtype expressed overall higher functioning, whereas the maternal uniparental disomy subtype performed more similarly to the ASD group. Results are the first to show deficits in social cognitive ability early in development. The severity and differences in deficits between PWS subtypes are important in informing early intervention efforts.

KEYWORDS: Autism spectrum disorder; Prader-Willi syndrome; Pretend play; Social cognition

PMID:31388797 DOI:10.1007/s10803-019-04152-4

Estival S, Krasny-Pacini A, Laurier V, Maugard C, Thuilleaux D, Postal V. Cognitive Training Targeting Planning Dysfunction in Adults with Prader-Willi Syndrome: Brief Report of a Study Protocol.Dev Neurorehabil. 2019 Jul 29:1-7.. [Epub ahead of print]

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a neurodevelopmental genetic disorder involving executive deficits notably with planning. The main objective of the study is to assess the effectiveness of cognitive training on daily life planning difficulties in PWS patients.
METHODS/DESIGN: The study is a double-blind randomized controlled trial which will compare the effectiveness of a metacognitive strategy intervention designed to improve planning difficulties for PWS patients to usual occupational therapy. Sixty adults will be included over 20 months. The main outcome measure will be the performance on the Modified Six Elements Test from the BADS; secondary outcome measures will be computerized executive tasks and questionnaires. Daily life planning difficulties will be identified and transformed into measurable goals using Goal Attainment Scaling.
DISCUSSION: The project will provide knowledge on the difficulties experienced by PWS patients, in relation to their executive functioning in order to implement effective intervention for planning in daily life.

KEYWORDS: Cognitive rehabilitation; Prader-Willi syndrome; executive functions; metacognitive strategy; planning; randomised controlled trial
PMID:31355692 DOI:10.1080/17518423.2019.1642414

Butler MG, Matthews NA, Patel N, Surampalli A, Gold JA, Khare M, Thompson T, Cassidy SB, Kimonis VE. Impact of genetic subtypes of Prader-Willi syndrome with growth hormone therapy on intelligence and body mass index. Am J Med Genet A. 2019 Jul 16. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a genomic imprinting disorder characterized by infantile hypotonia with a poor suck and failure to thrive, hypogenitalism/hypogonadism, behavior and cognitive problems, hormone deficiencies, hyperphagia, and obesity. The Stanford Binet and Wechsler (WAIS-R; WISC-III) intelligence (IQ) tests were administered on 103 individuals with PWS from two separate cohorts [University of California, Irvine (UCI) (N = 56) and Vanderbilt University (N = 47)] and clinical information obtained including growth hormone (GH) treatment, PWS molecular classes, weight and height. Significantly higher IQ scores ($p < .02$) were found representing the vocabulary section of the Stanford Binet test in the growth hormone (GH) treated group when compared with non-GH treatment in the pediatric-based UCI PWS cohort with a trend for stabilization of vocabulary IQ scores with age in the GH treated maternal disomy (UPD) 15 subject group. Significant differences ($p = .05$) were also found in the adult-based Vanderbilt PWS cohort with 15q11-q13 deletion subjects having lower Verbal IQ scores compared with UPD 15. No difference in body mass index was identified based on the PWS molecular class or genetic subtype. Medical care and response to treatment with growth hormone may influence intelligence impacted by PWS genetic subtypes and possibly age, but more studies are needed.

KEYWORDS: PWS molecular classes; Prader-Willi syndrome; Stanford Binet intelligence test; Wechsler intelligence test; body mass index; growth hormone treatment
PMID:31313492 DOI:10.1002/ajmg.a.61293