INTERNATIONAL PRADER-WILLI SYNDROME ORGANISATION

7TH SCIENTIFIC CONFERENCE

MAY 20-21, 2010, TAIPEI, TAIWAN

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SCIENTIFIC CONFERENCE COMMITTEE

Suzanne B Cassidy, M.D.

Dr. Cassidy is currently a Clinical Professor of Pediatrics at the University of California, San Francisco. She is a board certified Clinical Geneticist and Pediatrician whose career includes doing patient care, teaching for medical students, residents and advanced trainees, and clinical research mainly focused on Prader-Willi syndrome. She has also been the director of clinical genetics divisions at three medical schools in the past. She has conducted multi-disciplinary specialty clinics for Prader-Willi syndrome since 1981 and has published widely on her clinical observations and research on PWS. She has been the Chair of the Scientific Advisory Board of Prader-Willi Syndrome Association (USA) in the past, and remains on that board. And she has been the professional delegate to IPWSO from the USA since IPWSO was established. She has helped to organize several IPWSO and PWSA(USA) Scientific Conferences, and is a frequent speaker about PWS at local, regional, national and international educational and medical conferences related to PWS. She is coeditor of the book Management of Genetic Syndromes, now in its 3rd edition.

Leopold M.G. Curfs, PhD

Professor Curfs is director of the Governor Kremers Centre at the Academic Hospital and Maastricht University. He was rewarded with the 'Governor Kremers' professorship at the Faculty of Health, Medicine and Life Sciences of Maastricht University, a research chair in intellectual disability. He heads the program 'Intellectual Disabilities: a life cycle approach to valuing people' within the School for Public Health and Primary Care (Caphri) and the program 'Specific syndromes and mental retardation' within the research institute Growth & Development. His research is aimed at understanding mechanisms by which genes affect the neuropathological underpinning of cognitive and behavioral deficits. He has published and presented extensively on various aspects of Prader-Willi syndrome (PWS), most specifically the medical, behavioral and psychiatric disorders, and comparisons between genetic subtypes. He is actively involved in IPWSO, where he is a member of the Scientific Advisory Board. He has the chair of the Scientific Advisory Board of PWS in the Netherlands and is a member of the board of the Dutch Prader-Willi syndrome organisation. He has published and taught widely about PWS, helped to organize national and international conferences about PWS and is a frequent key-note speaker on PWS.

SCIENTIFIC CONFERENCE ADVISORY BOARD

Daniel Driscoll, M.D., Ph.D., Clinical Geneticist, USA
Tomoko Hasegawa, M.D., Clinical Geneticist, Japan
Anthony Holland, M.D., Psychiatrist, UK
Shuan-Pei Lin, M.D., Clinical Geneticist, Taiwan
Maïthé Tauber, M.D., Pediatric Endocrinologist, France
Duangrurdee Wattanasirichaigoon, M.D., Clinical Geneticist, Thailand

INVITED SPEAKERS

Daniel J. Driscoll, M.D., Ph.D. FAAP, FACMG
Dr. Driscoll is a Professor of Pediatrics and Genetics and Hayward Professor of Genetics Research at the University of Florida College of Medicine in Gainesville, Florida, USA, He has been conducting clinical and laboratory research on Prader-Willi syndrome since the late 80's and has been a major contributor to our understanding of the genetics of Prader-Willi syndrome and genomic imprinting in the PWS region as well as to elucidation of the natural history of Prader-Willi syndrome. He is widely published on PWS and a major spokesperson on PWS in the US and internationally. He is a member of the Board of Directors, Clinical Advisory Board (of which he is Chair) and has been on the Scientific Advisory Board for PWSA (USA), and is a member of the Scientific Advisory Board of IPWSO.

Maïthé Tauber, M.D.
Dr. Maïthé Tauber is a Professor of Pediatrics and head of Pediatric Endocrinology at Hôpital des Enfants in Toulouse, France. She is Coordinator of the French reference center for Prader-Willi syndrome and chair of the coordination of the French networks for prevention and care of childhood obesity. She chairs the scientific committee of the French PWS association. She has been active in research on obesity in general and in Prader-Willi syndrome, in particular, for many years, as well as being the coordinator of many studies on growth hormone. She is widely published on various aspects related to the manifestations and care of individuals with Prader-Willi syndrome. She was recently host to an international scientific meeting on Prader-Willi syndrome aimed at management of affected individuals and chaired the scientific committee for the writing of the recommendations for diagnosis and care of patients with PWS that was recently published.

Tsutomu Nakada, M.D., Ph.D., FAAN
Dr. Nakada has established a new research center at the Brain Research Institute, University of Niigata, Japan, where he is Chair and Professor in the Departments of Integrated Neuroscience, Functional Neurology and Neurosurgery, Biological Magnetic Resonance, and Digital Medicine. He is also on the faculty at the University of California in the US. He is board certified in Internal Medicine (Japan), Neurology (Japan and USA), Clinical Neurophysiology (USA), and Imaging (USA). He has been conducting both clinical and research work in the US and Japan related to neuroscience, and his group has published original research on brain findings in Prader-Willi syndrome. He was elected a council member of the Science Council of Japan in 2008.

Dick F. Swaab, M.D., Ph.D.
Dr. Swaab is Professor of Neurobiology at the Medical Faculty, University of Amsterdam in The Netherlands. He is the Founder and was long-time Director of the Netherlands Brain Bank. He is leader of the research team on Neuropsychiatric Disorders for the Netherlands Institute for Neuroscience. For his work, her received the Royal Honour, "Knight in the Order of the Netherlands Lion", bestowed by Queen Beatrix of the Netherlands in 1998. He has also received numerous scientific awards and has published over 450 papers and 190 book chapters as well as being editor of 24 books and series editor of the Elsevier Handbook of Clinical Neurology. One of his special areas of research interest is the hypothalamus, and he has made original important observations about the hypothalamus in Prader-Willi syndrome.

Stewart Einfeld, M.D.
Dr. Einfeld is Chair of Mental Health and Senior Scientist at the Brain and Mind Research Institute, University of Sydney, Australia. He is a Child Psychiatrist and is a principal investigator of the Australian Child to Adult Development Study, which includes 60 people with Prader-Willi syndrome. One of his special areas of interest and research is gene-to-behavior pathways in developmental disabilities and their consequences for families and communities. Dr. Einfeld is also a co-author of the Developmental Behaviour Checklist, which is widely used for assessment of mental health in developmental disabilities. He is conducting a number of treatment trials of autism and Prader-Willi syndrome.

7th International Prader-Willi Syndrome Organisation Scientific Conference
May 20-21, 2010; Taipei, Taiwan

Thursday, May 20

8:45-9:15 Opening Ceremony

9:15-9:30 Welcome to Scientific Conference
Leopold Curfs and Suzanne Cassidy

9:30-10:45 Session 1: Medical and Genetic Issues
Moderator: Shuan-Pei, Lin, MD (Taiwan)

9:30-10:00 **INVITED SPEAKER:** ***Daniel Driscoll (USA):***
Clinical and genetic overview of Prader-Willi syndrome

10:00-10:15 ***Margje Sinnema (Netherlands):***
Ageing in Prader-Willi syndrome

10:15-10:45 Coffee break

10:45-11:00 ***Ronnaug Saeves (Norway):***
Salivary flow and oral abnormalities in Prader-Willi syndrome

11:00-11:15 ***Toshiro Nagai (Japan):***
Frequency and risk factors for severe scoliosis in Prader-Willi syndrome

11:15-11:30 ***Tsutomu Ogata (Japan):***
Maternal age effects on the changing proportion of genetic causes of Prader-Willi syndrome in Japan

11:30 –11:45 ***María Eugenia Foncuberta (Argentina):***
Phenotype/genotype correlation in children with Prader-Willi syndrome

11:45-12:00 ***Anne Chun-Hui Tsai (USA):***
Patients with Prader-Willi syndrome coexist with other chromosomal anomalies: Pure coincidence? Or maybe not?

12:00-12:15 ***Daniel Driscoll (USA):***
Report from the Prader-Willi syndrome research strategy workshop, Bethesda, MD, USA, November, 2009

12:15 – 13:30 Lunch

13:30-15:00 Session II – Endocrine and Obesity Issues
Moderator: Peter Davies, PhD, (Australia)

13:30 – 14:00 **INVITED SPEAKER:** ***Maïthé Tauber (France)***
Endocrine dysfunction in Prader-Willi syndrome

14:00-14:15 ***Stense Farholt (Denmark):***
Normal cortisol response to high dose synathen and insulin tolerance test in children and adults with Prader-Willi syndrome

14:15-14:30 ***Graziano Grugni (Italy):***
Prevalence of central adrenal insufficiency in children and adolescents with Prader-Willi syndrome: Preliminary results

14:30-14:45 ***Antonino Crinó (Italy):***
Evaluation of growth hormone responsiveness to standard and combined provocative tests in very young children with Prader-Willi syndrome

14:45-15:00 ***Rasmus Sode-Carlsen (Denmark):***
Two year of growth hormone therapy improves body composition in adults with Prader-Willi syndrome

15:00 – 15:30 Coffee break

15:30-15:45 ***Graziano Grugni (Italy):***
Metabolic syndrome among adults with Prader-Willi syndrome

15:45-16:00 ***Alexander Viardot (UK):***
Exenatide (Byetta) increases postprandial fullness without side effects in Prader-Willi syndrome: A pilot study

16:00-16:45 ***Talia Eldar-Geva (Israel):***
Hypogonadism in Prader-Willi syndrome: A spectrum from primary gonadal to primary hypothalamic dysfunction

16:45-17:00 ***Yasuhiro Kido (Japan):***
Testosterone replacement therapy in 18 adult patients with Prader-Willi syndrome

17:00–19:00 Poster Session and Welcome Party
17:00 – 18:00 Presenters of odd numbered abstracts at their posters
18:00 – 19:00 Presenters of even numbered abstracts at their posters

19:00-21:00 Dinner for Scientists

Friday, May 21

8:00-9:30 Session III-Neurology
Moderator: Yi-Ning Su, MD, PhD (Taiwan)

8:00–8:30 **INVITED SPEAKER**: ***Tsutomu Nakada (Japan):***
Fetal to adult type brain conversion in the perinatal period

8:30-8:45 ***Ken-Ichi Yamada (Japan):***
Brain developmental differences in Prader-Willi syndrome detected by diffusion tensor imaging

8:45-9:00 ***Susanne Blichfeldt (Denmark):***
Hypotonia in neonates with Prader-Willi syndrome is not always seen at birth but becomes evident after the first days

9:00-9:30 **INVITED SPEAKER**: ***Dick Swaab (Netherlands):***
Gene expression in brain and premature Alzheimer disease

9:30-11:30 Session IV - Psychiatry and Behavior
Moderator: Anthony Holland, MD (UK)

9:30-10:000 **INVITED SPEAKER**: ***Stewart Einfeld (Australia)***
Update on Psychiatric Issues in PWS

10:00-10:30 Coffee break

10:30-10:45 ***Kate Woodcock & Leah Bull (UK):***
An examination of the underpinnings of a multi-level strategy for addressing the problem of temper outbursts in individuals with PWS and an initial evaluation of this strategy

10:45-11:00 ***Varda Gross-Tsur (Israel):***
Voluntary fasting in adolescents and adults with Prader-Willi syndrome

11:00–11:15 ***Joyce Whittington (UK):***
Recent mortality rates and risk of dementia in PWS

11:15-12:30 Session V - Databases for Prader-Willi syndrome
Moderator: Leopold Curfs, PhD (Netherlands)

11:15-11:30 ***Janalee Heinemann (USA:)***
PWSA (USA) family reported medical questionnaire results

11:30-11:45 ***Gweanelle Diene (France):***
Endocrine disorders in children with Prader-Willi syndrome--data from 226 children and adolescents of the French database

11:45-12:00 *Elly Scheermeyer (Australia):*
Setting up a national database to capture baseline and follow up data of children with PWS on GH in Australia and New Zealand 2009/10

12:00-12:15 *Anthony Holland (UK):*
The European Prader-Willi syndrome database: A tool to support research into a rare syndrome

12:15-12:25 Discussion: All database presenters

12:25-12:30 Closing comments

ORAL PRESENTATIONS

MEDICAL AND GENETIC ISSUES

CLINICAL AND GENETIC OVERVIEW OF PRADER-WILLI SYNDROME

Daniel J. Driscoll
Departments of Pediatrics and Molecular Genetics & Microbiology, University of Florida College of Medicine, Gainesville, FL, USA

AGEING IN PRADER-WILLI SYNDROME

Margje Sinnema[1,2], Marian A. Maaskant[2,3,4], Henny M.J. van Schrojenstein Lantman-de Valk[2,5], Constance T.R.M. Schrander-Stumpel[1], Leopold M.G. Curfs[1,2]
[1]Department of Clinical Genetics, Maastricht UMC; [2]Governor Kremers Centre, Maastricht University, Maastricht; [3]Department of Health Care and Nursing Science, Maastricht University; [4]Stichting Pergamijn, Echt; [5]Department of General Practice, Maastricht, The Netherlands

SALIVARY FLOW AND ORAL ABNORMALITIES IN PRADER-WILLI SYNDROME

Ronnaug Saeves[1], Hilde Nordgarden[1], Ivar Espelid[2], Kari Storhaug[1]
[1]TAKO-centre, Lovisenberg Diakonale Hospital, Oslo, Norway; [2] Department of Pediatric Dentistry, University of Oslo, Norway.

FREQUENCY AND RISK FACTORS OF SEVERE SCOLIOSIS IN PRADER-WILLI SYNDROME

Toshiro Nagai[1], Yutaka Nakamura[2], Masataka Kakihana[2], Kazuo Obata[1], Satoru Sakazume[1], Nobuyuki Murakami[1].
[1]Department of Pediatrics;[2]Department of orthopedics Dokkyo Medical University Koshigaya Hospital, Saitama Japan

MATERNAL AGE EFFECTS ON THE CHANGING PROPORTION OF GENETIC CAUSES OF PRADER-WILLI SYNDROME IN JAPAN

Keiko Matsubara[1,2], Yuki Kozu[2], Kazuo Obata[2], Nobuyuki Murakami[2], Tsutomu Ogata[1], Toshiro Nagai[2]
[1] National Research Institute for Child Health and Development, Department of Endocrinology and Metabolism, Tokyo, Japan; [2] Dokkyo Medical University Koshigaya Hospital, Department of Pediatrics, Koshigaya, Japan

PHENOTYPE/GENOTYPE CORRELATION IN CHILDREN WITH PRADER WILLI SYNDROME (PWS)

M. Foncuberta, S. Caino, V. Aráoz, K. Abraldes, V. Fano, L. Chertkoff , M. Torrado
Hospital de Pediatria "Prof. Dr. J.P. Garrahan". Buenos Aires. Argentina

PATIENTS WITH PRADER–WILLI SYNDROME COEXIST WITH OTHER CHROMOSOMAL ANOMALIES: PURE COINCIDENCE? OR MAYBE NOT?

Anne Chun-Hui Tsai, David K Manchester
Section of Clinical Genetics and Metabolism, Department of Pediatrics, University of Colorado School of Medicine, USA

REPORT FROM THE PRADER-WILLI SYNDROME RESEARCH STRATEGY WORKSHOP

Daniel J Driscoll[1], Uta Francke[2], Anthony Goldstone[3], Anthony Holland[4], Stephen O'Rahilly[5], Rachel Wevrick[6], Theresa V. Strong[7]
[1]Departments of Pediatrics and Molecular Genetics & Microbiology, University of Florida College of Medicine, Gainesville, FL, USA; [2]Departments of Genetics and Pediatrics, Stanford University, Palo Alto, CA, USA; [3]Metabolic and Molecular Imaging Group, MRC Clinical Sciences Centre, Imperial College, London, UK; [4]Department of Psychiatry and [5]Departments of Clinical Biochemistry and Medicine, University of Cambridge, Cambridge, UK; [6]Department of Medical Genetics, University of Alberta, Edmonton, Canada; [7]Departments of Medicine and Genetics, University of Alabama at Birmingham, Birmingham, AL, USA.

ENDOCRINOLOGY AND OBESITY

ENDOCRINE DYSFUNCTION IN PRADER-WILI SYNDROME

Maïthé Tauber
The French Reference Center for PWS, Toulouse, France

NORMAL CORTISOL RESPONSE TO HIGH DOSE SYNACTHEN AND INSULIN TOLERANCE TEST IN CHILDREN AND ADULTS WITH PRADER-WILLI SYNDROME

Stense Farholt[1], Rikke Juul Vestergaard[1], Helle Vinther[1], Rasmus Sode-Carlsen[1], Jens Sandahl Christiansen[2], John R. Østergaard[1], Charlotte Høybye[3]
[1]Centre for Rare Diseases, Department of Paediatrics, Aarhus University Hospital Skejby, Aarhus, Denmark; [2]Department of Endocrinology M, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden

PREVALENCE OF CENTRAL ADRENAL INSUFFICIENCY IN CHILDREN AND ADOLESCENTS WITH PRADER-WILLI SYNDROME: PRELIMINARY RESULTS

Graziano Grugni[1], Antonino Crinò[2], Andrea Corrias[3], Clotilde De Medici[1], Stefania Di Candia[4], Girolamo Di Giorgio[2], Alessandro Di Maio[1], Luigi Gargantini[5], Lorenzo Iughetti[6], Antonella Luce[7], Benedetta Mariani[4], Giuseppe Chiumello[4], Luciano Beccaria[8], Alessandro Salvatoni[7].
Dept. of Pediatrics of [1]Italian Auxological Institute, Verbania, Italy; [2]Bambino Gesù Hospital, Palidoro-Rome, Italy; [3]Regina Margherita Hospital, Turin, Italy; [4]S. Raffaele Hospital, Milan, Italy; [5]Civic Hospital of Treviglio (BG), Italy; [6]Univ. of Modena and Reggio Emilia, Italy; [7]A. Manzoni Hospital, Lecco, Italy; [7]Univ. of Insubria, Varese, Italy.

EVALUATION OF GROWTH HORMONE RESPONSIVENESS TO STANDARD AND COMBINED PROVOCATIVE TESTS IN VERY YOUNG CHILDREN WITH PRADER-WILLI SYNDROME

Antonino Crinò[1], Girolamo Di Giorgio[1], Sabrina Spera[1], Maria Cristina Matteoli[1], Guido Castelli Gattinara[1], Graziano Grugni,[2]
[1]Paediatric and Autoimmune Endocrine Diseases Unit, Bambino Gesù Children's Hospital Scientific Institute (IRCCS), Palidoro (Rome); [2]Italian Auxological Institute Foundation, Piancavallo (Verbania) - Italy

TWO YEARS OF GROWTH HORMONE THERAPY IMPROVES BODY COMPOSITION IN ADULTS WITH PRADER-WILLI SYNDROME

Rasmus Sode-Carlsen[1], Jens Bollerslev[2], Thomas Schreiner[2], Jens Sandahl Christiansen[3], Stense Farholt[1], Kai Fr. Rabben[4], Charlotte Höybye[5]
[1]Centre for Rare Diseases, Department of Paediatrics, Aarhus University Hospital Skejby, Aarhus, Denmark; [2]Department of Endocrinology, Rikshospitalet, Oslo, Norway; [3] Department of Endocrinology, Aarhus University Hospital, Aarhus, Denmark; [4] Frambu, Siggerud, Norway; [5] Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden

METABOLIC SYNDROME AMONG ADULTS WITH PRADER-WILLI SYNDROME

Graziano Grugni[1], Antonino Crinò[2], Andrea Corrias[3], Marco Cappa[2], Luigi Gargantini[4], Lorenzo Iughetti[5], Karen Marenzi[6], Claudio Pagano[7], Letizia Ragusa[8], Alessandro Salvatoni[9], Alessandro Sartorio[1], Giorgio Tonini[10], Roberto Vettor[7], Giuseppe Chiumello[6], Paolo Brambilla[11]
Dept. of Pediatrics of [1]Italian Auxological Institute, Verbania, Italy; [2]Bambino Gesù Hospital, Palidoro-Rome, Italy; [3]Regina Margherita Hospital, Turin, Italy; [4]Civic Hospital, Treviglio (BG), Italy; [5]University of Modena and Reggio Emilia, Italy; [6]S. Raffaele Hospital, Milan, Italy; [8]Oasi Maria S.S., Troina (EN), Italy; [9]University of Insubria, Varese, Italy and [10]Burlo Garofalo Hospital, Trieste, Italy. [7]Dept. of Internal Medicine, Padua, Italy; [11]ASL Milano 2, Milan, Italy.

EXENATIDE (BYETTA®) INCREASES POSTPRANDIAL FULLNESS WITHOUT SIDE EFFECTS IN PRADER-WILLI SYNDROME - A PILOT STUDY.

Alexander Viardot[1], Lisa Sze[2], Louise Purtell[3], Georgina Loughnan[4], Ellie Smith[5], Herbert Herzog[6], Amanda Sainsbury-Salis[6], Katharine Steinbeck[4], Lesley V Campbell[3]
[1]Department of Investigative Medicine, Imperial College, Hammersmith Campus, London,UK; [2]Clinics for Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich, Zurich, Switzerland, [3]Diabetes & Obesity Research Program, Garvan Institute of Medical Research, Sydney, Australia, [4]Prader-Willi Syndrome Clinic, Metabolism & Obesity Services, Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia, [5]Department of Cytogenetics, The Children's Hospital, Westmead Clinical School, Westmead, Australia, [6]Neuroscience Research Program, Garvan Institute of Medical Research, Sydney, Australia.

HYPOGONADISM IN PRADER-WILLI SYNDROME: A SPECTRUM FROM PRIMARY GONADAL TO PRIMARY HYPOTHALAMIC DYSFUNCTION

Talia Eldar-Geva[1], Varda Gross-Tsur[2], Fortu Benarroch[3], Orit Rubinstein[2], Harry J Hirsch[2]
[1]Reproductive Endocrinology and Genetics Unit, Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, the Hebrew University, Jerusalem, Israel; [2]Neuropediatric Unit, Department of Pediatrics, Shaare Zedek Medical Center, the Hebrew University, Jerusalem, Israel; [3]Child and Adolescent Psychiatry, Hadassah Mount Scopus Hospital, Jerusalem, Israel

TESTOSTERONE REPLACEMENT THERAPY IN 18 ADULT PATIENTS WITH PRADER-WILLI SYNDROME

Yasuhiro Kido, Kazuo Obata, Takayoshi Tsuchiya, Yuuzou Tomita, Nobuyuki Murakami, Toshiro Nagai
Department of Pediatrics, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan

NEUROLOGY

CONVERSION OF BRAIN CYTOSOL PROFILE FROM FETAL TO ADULT TYPE TAURINE-NAA EXCHANGE

Tsutomu Nakada
Departments of Integrated Neuroscience, Functional Neurology and Neurosurgery, Biological Magnetic Resonance, and Digital Medicine, Brain Research Institute, University of Niigata, Japan; Council Member, Science Council of Japan

BRAIN DEVELOPMENTAL DIFFERENCES IN PRADER-WILLI SYNDROME DETECTED BY DIFFUSION TENSOR IMAGING

Ken-ichi Yamada, Yuji Suzuki, Tsutomu Nakada,
Center for Integrated Human Brain Science, Brain Research Institute, University of Niigata, Japan

HYPOTONIA IN NEONATES WITH PRADER-WILLI SYNDROME IS NOT ALWAYS SEEN AT BIRTH BUT BECOMES EVIDENT AFTER THE FIRST DAYS

Susanne Blichfeldt
Department of Pediatrics, Glostrup University Hospital, Glostrup, Denmark

PRADER WILLI SYNDROME: GENE EXPRESSION AND PREMATURE ALZHEIMER DISEASE

D.F. Swaab[1], U.A. Unmehopa[1], B. Horsthemke[1], L.M.G. Curfs[2], F. Muscatelli[4]
[1]Netherlands Institute for Neuroscience, an Institute of the Royal Academe of science, Amsterdam, the Netherlands; [2]Institut für Humangenetik, Universitätsklinikum Essen, Essen, Germany; [3]Department of Clinical Genetics, Academic Hospital Maastricht and School of Oncology and Developmental Biology (GROW), Maastricht University, Maastricht and Governor Kremers Centre, Maastricht University, Maastricht; [4]INSERM U901/INMED, Parc Scientifique de Luminy, Marseille, France.

PSYCHIATRY AND BEHAVIOR

UPDATE ON PSYCHIATRIC ISSUES IN PRADER-WILLI SYNDROME

Stewart Einfeld
Department of Mental Health, Brain and Mind Research Institute, University of Syndey, Australia

AN EXAMINATION OF THE UNDERPINNINGS OF A MULTI-LEVEL STRATEGY FOR ADDRESSING THE PROBLEM OF TEMPER OUTBURSTS IN INDIVIDUALS WITH PWS AND AN INITIAL EVALUATION OF THIS STRATEGY

Kate A. Woodcock [1], Leah E. Bull [1], Tony Holland [2], Chris Oliver[1]
[1]Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, UK. [2]CIDDRG, Department of Psychiatry, Cambridge, UK

VOLUNTARY FASTING IN ADOLESCENTS AND ADULTS WITH PRADER WILLI SYNDROME.

Fortu Benarroch[1,2], Yehuda Pollak[1], Maayan Wertman[1], Larry Genstil[1], Harry J. Hirsch[1], Varda Gross-Tsur[1]
[1]Multidisciplinarry Clinic for PWS, Neuropediatric Unit, Department of Pediatrics, Shaare Zedek Medical Center, the Hebrew University, Jerusalem, Israel;
[2] Child and Adolescent Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

RECENT MORTALITY RATES AND RISK OF DEMENTIA IN PWS

Joyce Whittington, Tony Holland
University of Cambridge, Department of Psychiatry, Learning Disabilities Section, UK

DATABASES FOR PRADER-WILLI SYNDROME

PWSA (USA) FAMILY REPORTED MEDICAL QUESTIONNAIRE RESULTS

Janalee Heinemann[1], Barb McManus[2], Anne Chun-Hui Tsai[3]
[1]Prader-Willi syndrome Association (USA), Sarasota, FL, USA ; [2]Prader-Willi syndrome Association (USA), Sarasota, FL, USA ; [3]Clinical Genetics and Metabolism, Department of Pediatrics, University of Colorado School of Medicine, Denver, CO, USA

ENDOCRINE DISORDERS IN CHILDREN WITH PRADER-WILLI SYNDROME - DATA FROM 226 CHILDREN AND ADOLESCENTS OF THE FRENCH DATABASE

G. Diene, E. Mimoun, C. Molinas, M. Tauber
On behalf of the French Reference Centre for PWS

SETTING UP A NATIONAL DATABASE TO CAPTURE BASELINE AND FOLLOW UP DATA OF CHILDREN WITH PWS ON GH IN AUSTRALIA AND NEW ZEALAND 2009/10

Elly Scheermeyer[1], Mark Harris[2], Patricia Crock[3], Charles Verge[4], Geoff Ambler[5], George Werther[6], Philip Bergman[7], Jenny Couper[8], Catherine Choong[9], Paul Hofman[10], Mieke Van Driel[11], Peter Davies[12]

[1]The University of Queensland/[1*]Bond University, QLD; [2]Mater Hospital, QLD; [3]John Hunter Children's Hospital, NSW; [4]Sydney Children's Hospital, NSW; [5]The Children's Hospital at Westmead, NSW; [6]Royal Children's Hospital, VIC; [7]Monash Medical Centre, Vic; [8]Women's and Children's Hospital, SA; [9]Princess Margaret Hospital, WA; [10]Liggin's Institute, NZ; [11]Bond University, QLD; [12]Children Nutrition Research Centre, QLD.

THE EUROPEAN PRADER-WILLI SYNDROME DATABASE: A TOOL TO SUPPORT RESEARCH INTO A RARE SYNDROME

A. Holland[1], J. Whittington[1], O. Cohen[2], L. Curfs[3], B. Horsthemke[4], A.-C. Lindgren[5], C. Nourissier[6], N. Sharma[7], A. Vogels[8].

[1]Department of Psychiatry, University of Cambridge, UK [2]HC-Forum, Grenoble, France [3]University of Maastricht, Maastricht, The Netherlands [4]Institut für Humangenetik Essen, Germany [5]Karolinska Institute, Sweden [6]previously PWSA France [7]PWS Association (UK), Derby, UK [8]Catholic University of Leuven, Leuven, Belgium

POSTER PRESENTATIONS

(Left hand numbers correspond to poster number)

MEDICAL

1. **11 YEARS OF TREATMENT OF CHILDREN AT THE CENTRE FOR CHILDREN WITH PWS IN HILDESHEIM: RESULTS AND PROBLEMS**
   Constanze Laemmer
   Childrens Hospital St Bernward Krankenhaus Hildesheim, Germany

2. **BENEFITS OF A MULTI-DISCIPLINARY CLINICAL APPROACH TO PRADER-WILLI SYNDROME CHILDREN**
   Jennifer Donnelly, Sinead Archbold, Ohn Nyunt
   Department of Paediatric Endocrinology & Diabetes, Mater Children's Hospital, South Brisbane, Queensland, Australia

3. **ORTHOPAEDIC MANIFESTATIONS OF CHILDREN WITH PRADER WILLI SYNDROME**
   O. Nyunt[1], A. Gupta[2], M. Harris[1], J. Walsh[2], A.M. Cotterill[1]
   [1]Department of Paediatric Endocrinology and Diabetes,Mater Children's Hospital, Brisbane, Australia. [2]Department of Paediatric Orthopaedics, Mater Children's Hospital, Brisbane, Australia

4. **NEW ASPECT OF PEDIATRIC DENTISTRY FOR CHILDREN WITH PRADER-WILLI SYNDROME IN JAPAN**
   Yasuo Takeda, Osamu Nakanishi
   Department of Pediatric Dentistry, Kitakyushu Rehabilitation Center for Children with Disabilities, Japan

5. **UNINARY INCONTINENCE IN PERSONS WITH PRADER-WILLI SYNDROME**
   Margje Sinnema[1], Alexander von Gontard[2], Robert Didden[3], Leopold M.G. Curfs[1]
   [1]Department of Clinical Genetics, Maastricht University Medical Centre, Maastricht - Governor Kremers Centre, Maastricht University, The Netherlands; [2]Department of Child and Adolescent Psychiatry, Saarland University Hospital, Homburg, Germany; [3]Radboud University Nijmegen, Behavioural Science Institute, Nijmegen, and Trajectum, The Netherlands

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   Hospital de Pediatria "Prof. Dr. J.P. Garrahan". Buenos Aires. Argentina

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Margje Sinnema[1,2,5], Kees E.P. van Roozendaal[1], Marian A. Maaskant[2,3,4], Hubert J.M. Smeets[1,5], John J.M. Engelen[1,5], Nieke Jonker-Houben[1], Constance T.R.M. Schrander-Stumpel[1,5], Leopold M.G. Curfs[1,2,5]

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Wei Lu, Xiuli Chen, Feihong Luo, Dijing Zhi, Rong Ye, Li Xi, Shuixian Shen

Department of Endocrine and Metabolic Diseases, Children's Hospital of Fudan University, Shanghai, P.R. China

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Fanny Cortés [1,2], Nancy Unanue[1], Giannina Franco[1], Paula Velaszquez[1], Bernhard Horsthemke [3]

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Wei Wang, Xiaoyan Wu, Hongmei Song, Zhengqing Qiu, Min Wei

Department of Pediatrics, Peking Union Medical College Hospital, Peking Union Medical College, Beijing, China

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Chia-Cheng Hung[1,2], Shin-Yu Lin[3,4], Chien-Nan Lee[4], and Yi-Ning Su[1,2,3]
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Department of Pediatrics, Dokkyo Medical University Koshigaya Hospital, Japan

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Nobuyuki Murakami, Hisashi Itabashi, Yuji Oto, Kazuo Obata, Toshiro Nagai
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19. LONG-TERM GH THERAPY AND GLUCOSE METABOLISM IN ADULTS WITH PRADER-WILLI SYNDROME

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Louise Purtell[1], Lisa Sze[2], Georgina Loughnan[3], Ellie Smith[4], Herbert Herzog[5], Amanda Sainsbury[5], Katharine Steinbeck[3], Lesley V Campbell[1], Alexander Viardot[1]

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25. EXERCISE ON HAND – THE BENEFITS OF IN-HOME EXERCISE EQUIPMENT FOR PATIENTS WITH PRADER-WILLI SYNDROME

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26. BARIATRIC SURGERY IN PRADER-WILLI SYNDROME: LONG-TERM FOLLOW-UP AFTER BILIOPANCREATIC DIVERSION

Graziano Grugni[1], Girolamo Di Giorgio[2], Antonino Crinò[2]

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27. VAGUS NERVE STIMULATION IN CURBING HYPERPHAGIA IN PRADER-WILLI SYNDROME

Catherine J McAllister[1], Anthony J Holland[1], Howard A Ring[1], Nicholas Finer[2], Karl Sylvester[3], Paul C Fletcher[1], Nicholas W Morrell[3], Matthew R Garnett [3], Mark RA Manford [3]

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28. ARE THERE DIFFERENCES BETWEEN PEOPLE WITH PRADER-WILLI SYNDROME AND HEALTHY CONTROLS IN HEART RATE VARIABILITY PARAMETERS IN RESPONSE TO EATING-RELATED PICTURES?

Hubert Soyer[1], Svetlana Labun[1], Arne Wittling[2], Elisabeth Schweiger[2]
[1]Regens Wagner, Absberg, Germany; [2]Center for Neuropsychological Research, University of Trier, Germany.

29. POLYSOMNOGRAPHY IN ADULT OBESE SUBJECTS WITH AND WITHOUT PRADER-WILLI SYNDROME

Paolo Fanari[1], Graziano Grugni[2], Lorenzo Priano[3], Mauro Cornacchia[1], Ilaria Tovaglieri[1], Franco Codecasa[1], Alberto Salvadori[1]
[1]Department of Pulmonary Rehabilitation; [2]Department of Neurology; [3]Department of Auxology, IRCCS Istituto Auxologico Italiano, Piancavallo (VB), Italy

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P. Bregani, I. Achutegui
Paediatrics Department, IRCCS San Raffaele Scientific Institute, Milan, Italy

31. RELATIONSHIP BETWEEN PEOPLE WITH PWS AND THEIR SIBLINGS: PARENTS REPORT

I. Achutegui, P. Bregani, V. Pogliani, D. Bettoni, O. Fontana
Paediatrics Department, IRCCS San Raffaele Scientific Institute, Milan, Italy

32. INTERPERSONAL RELATIONSHIPS AMONG ADULTS WITH PRADER-WILLI SYNDROME RESIDING IN GROUP HOMES

Winfried Schillinger[1], Janice Forster[2], Hubert Soyer[1].
[1]Regens Wagner, Absberg, Germany; [2]Pittsburgh Partnership, Pittsburgh, PA, USA.

33. PERSONS WITH PWS HAVE RESEMBLANCES TO AND DIFFERENCES FROM PERSONS WITH ASPERGER SYNDROME. ARE THE RESEMBLANCES FROM AUTISTIC TRAITS?

Tomoko Hasegawa
Genetic Support and Consultation Office, PWSA Japan

34. AUTISM AND PRADER-WILLI SYNDROME: LITERATURE REVIEW AND THE BASIS OF A RESEARCH PROJECT

C. Mantoulan[1], M. Glattard[1], P. Payoux[2], G. Diene[1], I. Unsaldi[3], C.Molinas[1], B. Rogé[3], M. Tauber[1]

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35. DEMENTIA IN A WOMAN WITH PRADER-WILLI SYNDROME

Margje Sinnema[1,2], Constance T.R.M. Schrander-Stumpel[1], Hans E.G. Verheij[3], Mireille Meeuwsen[3], Marian A. Maaskant[2,4,5], Leopold M.G. Curfs[1,2]

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36. TREATMENT OF RECTAL PICKING BEHAVIOR IN PWS WITH SENSORY STIMULATION

Patrice Carroll[1], Janice Forster[2] and Linda Gourash[2]

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ABSTRACTS OF ORAL PRESENTATIONS

INVITED SPEAKER:

CLINICAL AND GENETIC OVERVIEW OF PRADER-WILLI SYNDROME

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Prader-Willi syndrome (PWS) is the most frequently diagnosed genetic cause of obesity. It also was the first recognized human disorder related to genomic imprinting. PWS occurs by one of three main mechanisms resulting in the failure of expression of genes located on the paternally inherited chromosome 15: 1) paternal deletion of the 15q11.2 region; 2) maternal uniparental disomy of chromosome 15 or 3) a defect in the imprinting process in 15q11.2.

The obesity in PWS typically begins between 2-4 years of age if the diet is not appropriately managed. Remarkably, as neonates there is an almost complete absence of an appetite drive. The appetite gradually increases in infancy and early childhood such that by about 8 years of age the individual with PWS has an insatiable appetite. Through careful longitudinal studies we have been able to discern 6 distinct nutritional phases in PWS. This makes PWS an ideal model system to dissect the various metabolic and hormonal components in appetite regulation and the development of obesity.

In addition, PWS affects a number of other body systems including endocrinologic, pulmonary, orthopedic, gonadal, cognitive, behavioral, ophthalmologic, dermatologic and gastrointestinal. Early diagnosis is important for effective long-term management and prognosis in this highly variable disorder.

AGEING IN PRADER-WILLI SYNDROME

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AIM: Little is known about the ageing process in persons with Prader-Willi syndrome (PWS). The aim of this study is to increase the knowledge about health in adults with PWS.
METHOD: Data regarding morbidity, behaviour and psychiatry of 102 adults with PWS (age range 18-66 yrs) were collected through semi-structured interviews. Medical data were retrieved from physicians.
RESULTS: Genetic testing showed 55 persons (54%) with a paternal deletion, 44 persons (43%) with a mUPD and 3 persons (3%) with a defect of the imprinting center. The observed distribution in our study differed from the literature (70% deletion, 30% mUPD), and was statistically significant (z-score: $p<0.05$). This was mainly due to a higher proportion of mUPD in the advanced age groups. Results showed that morbidity in adults with PWS is striking. The majority (56%) of adults with PWS were obese (BMI>30). Diabetes mellitus (17%), hypertension (9%), leg edema (56%), erysipelas (38%), osteoporosis (16%), pneumonia (14%) and constipation (38%) were common. Psychiatric episodes were present in 37/97 persons, mainly psychosis and affective disorders. The results on obesity-related problems, psychiatry, dermatology, genetics and the ageing process in general will be discussed during the presentation.
CONCLUSION: Our study population had a much broader age range, compared to other studies, because of a predominance of elderly people (40+) with PWS. In other studies these elderly persons might have been undiagnosed and/or underreported, due to a lack of genetic diagnosis. The results of this study serve as baseline information for further longitudinal research on the ageing process in PWS. The information will be used to adjust guidelines for preventive management.

SALIVARY FLOW AND ORAL ABNORMALITIES IN PRADER-WILLI SYNDROME

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INTRODUCTION: Persons with Prader-Willi syndrome (PWS) have sparse, thick and sticky saliva. High caries activity, poor oral hygiene and extreme tooth wear have been described in case reports. Oral and dental problems have received little attention by researchers. The aims of the study were to examine salivary flow rate and describe oral and dental characteristics in Prader-Willi syndrome.
METHODS: Fifty-one individuals with PWS, aged 5-41 years and an age and sex-matched control group were examined with regard to salivary flow rates, dental caries experience, gingival inflammation, enamel defects and tooth wear. Both unstimulated and chewing stimulated whole saliva as well as taste-stimulated parotid salivary flow rates were measured. The presence or history of dental caries was evaluated both clinically and on radiographs. Tooth wear was evaluated according to a 4-point scale, the Jonkoping-index. An individual tooth wear index (I_A) was created on the bases of the scores of incisal or occlusal wear for each tooth.
RESULTS: The average flow rate for unstimulated saliva (UWS) was 0.12±0.10 ml min^{-1} for individuals with PWS compared with 0.32 ± 0.20 ml min^{-1} for controls ($p<0.0001$). Chewing stimulated flow rate (SWS) was 0.41±0.35 ml min^{-1} for the PWS group compared with 1.06±0.65 ml min^{-1} for the control group ($p<0.0001$). Taste-stimulated parotid saliva was not found to differ significantly between the persons with PWS and healthy controls. There was no significant difference in caries experience in the primary dentition. Caries experience in permanent teeth (persons >18 years) was higher in the control group ($p=0.04$). The median GI-index (gingival inflammation) was significantly higher in the PWS group compared with the control group ($p=0.04$). The number of surfaces affected with enamel defects was 3.5(1.0-8.8) in the study group and 4.0(0.5-7.0) in the control group ($p=0.76$). The median tooth wear index I_A was 7.5 (0-100) in the PWS-group and 2.2 (0-10.7) in the control group ($p<0.0001$)
CONCLUSIONS: Low whole salivary flow and tooth wear are very common in individuals with PWS. Taste-stimulation may increase salivary flow rates in this group. The oral hygiene in the studied population with PWS was generally poor but the dental caries experience was not increased. This may reflect a low sugar diet and tight follow-up regimes.

FREQUENCY AND RISK FACTORS OF SEVERE SCOLIOSIS IN PRADER-WILLI SYNDROME

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INTRODUCTION: The frequency of scoliosis in Prader-Willi Syndrome (PWS) is known to be as high as 50 to 80%, but the frequency of severe scoliosis and risk factors for progression of scoliosis have not been reported.
PURPOSES & METHODS: The purposes of this study are two folds. First, we investigated the frequency of scoliosis (Cobb angle >10°) and incidence of severe scoliosis (Cobb angle >40°). Second, in order to find out the risk factors exacerbating scoliosis, we classified scoliosis according to the shapes and evaluated the prognosis.
SUBJECTS: One hundred fifty-six patients with PWS (median age: 12 years (1-53); genotypes: deletion 115 patients, uniparental disomy (UPD) 36, imprinting center (IC) abnormality 2, chromosomal aberration 3) were investigated.
RESULTS: Sixty-four patients had scoliosis (41%, Cobb angle>10°) and 16 of them showed severe scoliosis (10%, Cobb angle >40°). The frequency of scoliosis increased with age. No significant differences in frequency of scoliosis were seen by sex and genotypes. The shape of scoliosis was classified into 3 types: lumbar-curve, thoracic-curve and double-curve. Lumber-curve type included 36 patients; all patients except one showed left convex with severe scoliosis in 2. Thoracic-curve type included 6 patients; all showed right convex with severe scoliosis in 2. Double-curve type included 22 patients; all showed a right-thoracic and a left-lumbar curve with severe scoliosis in 12.
DISCUSSION: The frequency of scoliosis in Japanese patients was 41 % which was lower than that of Caucasian. The frequency of severe scoliosis was about 10 % of all patients (16/156 patients) and 25% of the patients with scoliosis (16/64 patients). With respect to the shape of scoliosis lumbar type was the most common and double-curve type had a tendency of rapid progression. All of these patients with severe scoliosis had surgical indication. About half (12/22 patients) of the double-curve type showed severe scoliosis indicating that this type should be carefully monitored.

MATERNAL AGE EFFECTS ON THE CHANGING PROPORTION OF GENETIC CAUSES OF PRADER-WILLI SYNDROME IN JAPAN

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INTRODUCTION: Microdeletion of the paternally inherited 15q11-13 imprinted domain and upd(15)mat are known to occur in ~70% and ~25% of Prader-Willi syndrome (PWS) patients, respectively. However, Whittington et al. (2007) have reported an increase in the frequency of upd(15)mat among the children aged under 5 years in the UK, with the frequencies of microdeletions and upd(15)mat being 44% and 50%, respectively. This phenomenon may be due to advanced maternal age that is widely observed in developed countries, because upd(15)mat usually result from trisomy rescue, and advanced maternal age is a risk factor for the development of trisomies such as Down syndrome. To examine this possibility, we studied Japanese patients with PWS.
METHODS: We performed methylation test, FISH, MLPA, and microsatellite analysis for 153 patients with PWS with normal karyotype (F:M 96:57, 0–53 years), and classified them into four types: (1) deletion type, (2) trisomy rescue type disomy, (3) monosomy rescue type disomy, and (4) other imprinting defects. Then, we compared the data from 103 patients born at or before 2002– (GrI) and 50 patients born in the period 2003–2009 (GrII).
RESULTS: In GrI, 85 (83%) had microdeletions, 14 (13%) had trisomy rescue type disomy, and 3 (3%) had monosomy rescue type disomy. In GrII, 30 (60%) had microdeletion, 14 (28%) had trisomy rescue type disomy, and 3 (6%) had monosomy rescue type disomy. The frequencies of microdeletion and trisomy rescue type disomy were significantly different between the two groups (P=0.001). There was significant difference in the maternal age at birth between the two groups (median 30, range 19–48 vs. median 35, range 23–45, P=0.0004). Between microdeletions and trisomy rescue type disomy, maternal age at birth was similar (P=0.063) in GrI but was significantly different in GrII (P=2.5E-06).
DISCUSSION: These results suggest that advanced maternal age is a risk factor for the development of trisomy rescue type upd(15)mat in GrII. Although the difference in the maternal age at birth was significantly different between the two different time periods, further investigations will be required to assess the maternal age effect on the development of trisomy rescue type upd(15)mat.

PHENOTYPE/GENOTYPE CORRELATION IN CHILDREN WITH PRADER WILLI SYNDROME (PWS)

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INTRODUCTION: PWS is a multisystemic disorder with a complex etiology: paternal deletion type I and II, maternal uniparental disomy (mUPD) and imprinting defects. There are several clinical–etiologic correlation studies between deletion and mUPD in patients with PWS, few of them distinguish between deletions type I and II.
Here we report a large clinical-etiologic correlation study considering deletion I, II and UPDm in children with PWS.
SUBJECTS AND METHODS: 146 PW patients (70/76 F/M) diagnosed by Southern Blot methylation test. The genetic subtypes were established using MLPA technique and microsatellite analysis. The clinical evaluation was based on Holm's criteria. Anthropometric measures evaluated: weight, height, sitting height, head circumference, BMI and parental height. IQ and adaptative behavior (AB) were performed using Wechsler and Vineland tests. Presence of seizures and puberty signs were also registered. Statistic Tests: ANOVA, χ^2, Fisher, Mann-Whitney.
RESULTS: Genetic subtypes were recognized in 146 affected children: 38 individuals carried deletion I, 44 deletion II and 64 UPDm. Considering Holm's criteria, hypopigmentation ($p<0.0001$) and sleep disturbance/apnea ($p=0.049$) were higher in the deleted group and no differences were found between deletion subtypes. Similar results were found for the presence of seizures. The three genetic groups did not shown differences for IQ and AB measures, mean z score of birth weight, weight, height, sitting height and BMI. Conversely, obesity (BMI>2SD) was more common in girls ≥3 years with deletion II ($p = 0.03$). Puberty signs in girls ≥ 8 years were also more frequent in this group ($p=0.012$). On the other hand, the mean head circumference z score, was lower in the deletion I group ($p=0.002$).
CONCLUSION: This study provides new data about the phenotypic differences among etiologic subtypes in children with PWS.

PATIENTS WITH PRADER–WILLI SYNDROME COEXIST WITH OTHER CHROMOSOMAL ANOMALIES: PURE COINCIDENCE? OR MAYBE NOT?

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INTRODUCTION: Prader–Willi syndrome (PWS) is a complex multisystem disorder characterized by neonatal hypotonia, developmental delay, short stature, obesity, behaviour problems, hypothalamic hypogonadism, and characteristic appearance. A number of sex chromosome abnormalities have been reported in children with (PWS). With an incidence of 1 in 500–1,000 for 47,XXY [Allanson and Graham, 2002] and 1 in 10,000–20,000 for PWS [Spinner and Emanuel, 2002] these two conditions would be expected to occur together by chance alone in 1 in 5 million to 20 million live births. In order to assess whether the co-occurrence of these two conditions in a patient might be related or due to coincidence, we performed an institutional database search for PWS coexistent with other chromosomal anomalies.

METHODS: From 1997-2008, 65 patients with PWS were seen in the out-patient Genetics Clinics and in-patient services of the Children's Hospital, a tertiary referral center. Medical records were reviewed and all PWS patients had high resolution karyotype, methylation, FISH and UPD studies where indicated.

RESULTS: Three patients aged 7. 19 and 21 were found to have PWS syndrome with other chromosomal anomalies. Patient one has PWS due to maternal UPD and 47, XXY; patient 2 has 22q11.2 deletion and PWS due to microdeletion; patient 3 has 8p23.1 deletion and PWS due to microdeletion. Of interest, one patient, age 13, was found to have Angelman syndrome due to UPD and XYY. 3/65 is far higher than the expected incidence by chance alone. Our patients were ascertained at various ages instead of all as newborns, therefore this does not reflect the true incidence. Clinical manifestations are more complicated in the 2 patients with other microdeletions, and the final height is taller in the patient with sex chromosomal anomalies.

DISCUSSION: Review of the literature found 9 cases of PWS with 47, XXY; three of PWS with 47, XXX and two with 47, XYY. Taken together with our data, we hesitate to attribute this to a genetic coincidence. Our PWS patient with maternal UPD 15 and XXY seemed to suggest nondisjunction occured twice in this individual. The patient with Angelman syndrome and XYY leads to the observation that paternal UPD happened twice. Our two patients with 2 microdeletions on different chromosomes suggested chromosomal instabilityin LCR regions can occur more frequently in certain individuals, who may have a genetic predisposition. However, 2 reported patients (Geffroy et al., 1998; Nowaczyk et al., 2004) had a paternally derived microdeletion of chromosome 15q11 and an extra X chromosome was shown to be derived from maternal nondisjunction. Although the mechanism of UPD and LCR through NHNJ seemed different, its coexistence seemed reasonable according to new concepts of copy number variation in human beings. Non-homologous end-joining mechanisms are well known, but recent models focus on perturbation of DNA replication and replication of non-contiguous DNA segments. For example, cellular stress (from nondisjunction or leading to nondisjunction) might induce repair of broken replication forks to switch from high-fidelity homologous recombination to non-homologous repair, thus promoting copy number change, or microdeletion. Our data also suggest that microarray is a more appropriate test for the diagnosis of PWS than classic HRS and FISH.

REPORT FROM THE PRADER-WILLI SYNDROME RESEARCH STRATEGY WORKSHOP

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Advances in the fields of genetics, appetite control, and neurobiology have established the foundation for understanding and more effectively treating Prader-Willi syndrome (PWS), but critical questions in basic and clinical science remain unresolved. A recent workshop (*The Prader-Willi Syndrome Research Strategy Workshop*, November 15-17, 2009) brought together a diverse group of clinical and basic scientists to discuss the strengths, opportunities, gaps in knowledge, and resources needed to advance the science of PWS. The Workshop was sponsored by the US National Institutes of Health, the Canadian Institutes of Health Research, and patient advocacy groups, including the Foundation for Prader-Willi Research (FPWR), the Prader-Willi Syndrome Association (USA) and FPWR-Canada.

Workshop participants focused on five areas of emphasis relevant to PWS: Emerging Clinical Issues, Obesity and Energy Balance, Mental Illness and Psychopathology, Molecular Genetics, and Animal Models. For each area, the current state of knowledge was reviewed, and basic and clinical research questions were prioritized. Overarching needs identified by participants included more detailed analysis of the variability of phenotype across individuals and along the developmental spectrum, the application of new technology to better characterize transcripts in the Prader-Willi critical region and to delineate the function and targets of the snoRNAs, and the use of mouse and human in vitro models for molecular target definition. Additional research focused on the neurobiology of appetite in PWS, including the changes associated with the shift from failure to thrive to hyperphagia was also recommended. A strong need to develop standardized measures for evaluation of animal models and for defining behavioral problems and mental illness was emphasized. Recommendations for resource development were also made.

Finally, it was recommended that multidisciplinary working groups be convened to provide recommendations on advancing candidate anti-obesity and psychiatric interventions into clinical trials, with special attention to defining informative surrogate endpoints, designing trials with sufficient power to demonstrate efficacy, and consideration of the unique ethical, medical, and logistical challenges that arise in performing clinical trials in this population. Enhanced multidisciplinary and international collaboration will be critical to effectively moving the field forward.

INVITED SPEAKER

ENDOCRINE DYSFUNCTION IN PRADER-WILI SYNDROME

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Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 including several endocrine dysfunctions whose pathophysiology and prevalence are not well documented.

The pathophysiology of the endocrine dysfunctions observed in PWS suggest hypothalamic impairment, which may explain hyperphagia due to a deficit of satiety, growth hormone deficiency (GHD), hypogonadism, hypothyroidism, and ocytocin deficicency . Hypothalamic dysfunction is probably related to pituitary hypoplasia and other MRI abnormalities of this brain region. Mouse models, particularly Necdin knock-out mice, support this hypothesis, showing a reduced number of oxytocin-containing neurons in the PVN and of luteinising hormone releasing hormone-containing neurons in the pre-optic. Moreover these hypothalamic abnormalities are also associated with autonomic nervous system impairment including vagal tone defect .

More recent findings : It has been recently reported that hypogonadism may result from a central and/or gonadal defect in men as in women. Elevated ghrelin levels were demonstrated in 2002 in PWS and we showed that they were present early in life, thus preceeding hyperphagia. Nevertheless, succesful decrease of ghrelin levels obtained in children, as in adults, using somatostatin analogs failed to induce weight loss and significant reduction of appetite. The exact reason for the early elevated circulating ghrelin is not known. It may be that therapeutical interventions need to be implemented in early life. In addition, the suggested role of hyperghrelinemia in GHD has not been clearly demonstrated. Knowledge of glucose metabolism impairment,, metabolic syndrome and diabetes in PWS is increasing and it seems likely that these dysfunctions are more frequent than previously thought in this population. The role of GH treatment in this pathophysiology is under investigation. Recent brain imaging techniques may help in understanding the area involved in hyperphagia and particularly the connections between the hypothalamus and the mesolimbic network.

The prevalence of endocrine dysfunction has been difficult to assess and the recent implementation of national patient databases does result in great help, albeit the well known lack of exhaustivity of these data collections. In our population, 40% of the children were overweight or obese. Growth hormone deficiency was present in 80% of children and 86.7% were treated, with a height gain of +1 SD and a BMI reduction of -0.8 Z-score achieved in the first year of treatment. Among patients younger than 2 years, 46% receive GH treatment. Hypogonadism was present in 49% of the patients, and hypothyroidism in 24.4%. Glucose intolerance was found in 4% of patients, but no diabetes mellitus was detected in the 74 patients who underwent endocrine investigation.

Set up of large international databases and pathophysiological collaborative research projects are needed in order to increase our knowledge, which may lead to specific treatment at the right time.

NORMAL CORTISOL RESPONSE TO HIGH DOSE SYNACTHEN AND INSULIN TOLERANCE TEST IN CHILDREN AND ADULTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Prader-Willi syndrome (PWS) is associated with hypogonadism and partial growth hormone insufficiency, which are thought to be partly explained by hypothalamic dysfunction. In addition partial insufficiency of the hypothalamic-pituitary-adrenal axis has recently been suggested (de Lind van Wijngaarden et al, 2008). They found an insufficient response to an overnight single-dose metyrapone test in 15 out of 25 (60%) randomly selected children with PWS.
OBJECTIVE: The aim of the present study was to further explore the above mentionned potentially dangerous condition in PWS by means of usual clinical tests for adrenal insufficiency.
METHODS: During a one-year period all PWS patients attending our out-patient clinic for rare diseases were consecutively enrolled. All were clinically and genetically verified as having PWS (34 deletions, 11 UPD, 2 ID, 10 methylation positive). Twenty-nine women and 22 men, median age 22 years (range 0.5-44 years) and median BMI 22.6 kg/m^2 (range 13.6-42.7 kg/m^2), were examined with a standard high dose synacthen test (HST). Two women and 6 men, median age 26 years (range 16-36 years) and median BMI 30.1 kg/m^2 (range 22.7-53.0 kg/m^2), were examined with a standard insulin tolerance test (ITT). Two out of these 8 persons were also tested using the HST. In case of admittance to our department with acute illness a spot cortisol was measured. Four adults had diabetes (two Type 1). One child and 2 adults had hypothyreosis. Thirty-seven were treated with growth hormone and 16 were treated with sex steroids. None were treated with systemic hydrocortisone.
RESULTS: Median cortisol in the HST at t=0 was 179 nmol/L (range 58-1020 nmol/L), and at t=30min was 698 nmol/L (range 474-1578 nmol/L). Three had a cortisol level less than 550 nmol/L at t=30min, and one of them even less than 500 nmol/L. In the latter ITT showed a normal peak cortisol of 583 nmol/L. Using the ITT the median cortisol at t=0 was 188 nmol/L (range (175-281 nmol/L), and the median cortisol at t=30min was 668 nmol/L (range 502-822 nmol/L).
During the study period three children were admitted to the acute ward at our hospital. Two had febrile illness (age 0.42 and 1 year), and one had a first episode of status asthmaticus (age 4 years). The spot cortisol were 1372, 775 and 1080 nmol/L, respectively.
CONCLUSION: In this cohort of 57 children and adults with PWS we were not able to confirm the finding by de Lind van Wijngaarden et al that patients with PWS are at an increased risk of having central adrenal insufficiency. Clinically significant insufficiency of the hypothalamic-pituitary-adrenal axis in PWS is rare.

PREVALENCE OF CENTRAL ADRENAL INSUFFICIENCY IN CHILDREN AND ADOLESCENTS WITH PRADER-WILLI SYNDROME: PRELIMINARY RESULTS

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INTRODUCTION: Retrospective studies estimated yearly mortality rates in Prader-Willi syndrome (PWS) to be 3% across all ages, with most deaths due to complications conventionally related to obesity. The etiology of the increased mortality seen in PWS, however, is not completely known and an awareness is arising that critical illnesses and sudden death of PWS patients may not be caused by obesity alone. In this context, a high prevalence of central adrenal insufficiency (CAI) during a metyrapone test in children with PWS has been recently reported (de Lind van Wijngaarden et al., J Clin Endocrinol Metab 2008). Nevertheless, data on the hypothalamic-pituitary-adrenal axis (HPA) in PWS are still controversial (Nyunt et al., ESPE 2009). Because adrenal insufficiency is a life-threatening disease, its diagnosis should be precise, urgent and reliable. Although the diagnosis of overt adrenal failure is generally easy, identification of asymptomatic patients with subtle dysfunction of the HPA is still a diagnostic challenge. In this light, Low Dose Short Synachten Test (LDSST) has been proposed to be highly sensitive in the evaluation of the integrity of the HPA in patients with CAI. Based on these data, we sought to explore the prevalence of CAI during a LDSST in a group of children and adolescents with PWS.
METHODS: Thirty-eight subjects with PWS, 23 males and 15 females, aged 1.1-15.7 yr (mean±SE: 6.0±0.7), were studied. Fifteen patients had del15q11-13, while UPD15 was found in 10 patients and a positive methylation test was demonstrated in the remaining 13 subjects. Baseline morning ACTH and cortisol were measured, following which, the LDSST started with the i.v. injection of 1 µg tetracosactrin (Synacthen, Biofutura Pharma, Italy). Blood samples for cortisol determination were taken at 0, 30 and 60 min. According to current literature (Maghnie et al, Eur J Endocrinol 2005), we have taken into consideration a cortisol peak response to LDSST less than 20 µg/dl for diagnosing CAI.
RESULTS: Basal ACTH and cortisol levels were 22.3±2.3 ng/L (nv: 8-50 ng/L) and 12.8±1.1 µg/dl (nv: 5-25 µg/dl), respectively. The mean peak cortisol after LDSST was 31.3±1.5 µg/dl, and the average increase from baseline was 18.6±1.1 µg/dl. Thirty-six patients showed normal cortisol response to LDSST; 2 subjects had evidence of CAI (5.2%).
DISCUSSION: The frequency of CAI was lower in our group of PWS than those previously reported. This finding is probably due to the different stimulation test adopted in our study. In this regard, previous data support the view that LDSST is a simple, reproducible, and sensitive test. However, the diagnostic value of tests to evaluate CAI is controversial, and none of the tests employed can be considered fully reliable. Consequently, further studies are warranted in order to better analyze the prevalence of CAI in PWS. In this light, we suggest that all patients with PWS undergo endocrine evaluation to determine if adrenal insufficiency is present.

EVALUATION OF GROWTH HORMONE RESPONSIVENESS TO STANDARD AND COMBINED PROVOCATIVE TESTS IN VERY YOUNG CHILDREN WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Growth hormone deficiency (GHD) has been demonstrated in the majority of patients affected by Prader-Willi syndrome (PWS). GH releasing hormone-plus-arginine (GHRH + ARG) test has been found reliable for the diagnosis of GH deficiency, both in children and adults with congenital hypopituitarism. GHRH+ARG is a validated GH stimulation test in adult PWS patients. GHRH plus piridostigmine (PD) test has been already used for the diagnosis of GHD in PWS patients and is considered similar to GHRH + ARG test. The reduced responsiveness to both these combined tests in adult PWS patients does not seem to be an artefact of obesity. The aim of this study was to evaluate the GH secretory pattern in very young PWS children and to verify if a combined administration of GHRH+ARG or PD could be a useful tool for the diagnosis of GHD.
METHODS: We enrolled 27 patients (12 F and 15 M) with genetically confirmed PWS (19 had a deletion and 8 had UPD of chromosome 15), aged 2.3±1.3 years (range 0.5-5 years), height-SDS -1.3±0.9 (range -2.5 -1 SDS), BMI-SDS 0.4±1.6 (range -2.9-2.9 SDS). Only three patients out of 27 were obese. Nobody was on treatment or was treated with GH. All subjects underwent clonidine (CLO, 150 mcg/m² orally) and arginine (0.5 gr/kg iv) tests (cut-off: 10 ng/ml) and GHRH (1 mcg/kg iv) plus PD (60 mg orally) test (14 patients) or GHRH plus ARG test (13 patients) (cut-off: 20 ng/ml). IGF1 levels were also measured (n.v.: >80 ng/ml).
RESULTS: Serum IGF-1 levels were low in 24/27 (89%) patients (45.3 ± 37.5; range 5-191 ng/ml.). GH peak was low in 24/27 (89%) and in 21/27 patients (78%) after CLO (6.1±4.3; range 6-18.3 ng/ml) and ARG (7.7 ±5.9; range 0.6-27 ng/ml) tests, respectively. Twenty patients out of 27 (74%) showed a low response to both standard tests and low IGF-1, meanwhile five patients (18.5%) showed a normal response to one of the standard tests. Only two patients showed normal response to both standard tests (7.5%) (they showed simultaneously normal response to combined tests, but low IGF-1). GH peak after combined test (31.3±11.2; range 1.3-40 ng/ml) was normal in 22/27 patients (81.5%) and low in five patients (18.5%) showing also low GH peak to both standard tests and low IGF-1. GH peak after GHRH+ARG test (mean: 36.6±6.7 ng/ml) was higher than after GHRH+PD (mean: 26.4±12.6 ng/ml) (p=0.0155). No correlation was found between BMI and GH peak, meanwhile a mild positive correlation was found between BMI and IGF-1 (n 27, r =0.4, p=0.035). Patients with deletion had higher GH peak after CLO (p=0.027) and after combined test (p=0.048) than patients with UPD.
DISCUSSION: Most PWS patients (74%) showed GHD confirmed by low GH peak to both standard tests and low IGF-1. At the same time most of patients (81%) showed a normal response to the combined test. These results demonstrate that the majority of PWS children have a hypothalamic defect with a normal GH pituitary reserve. Some studies concerning adult PWS patients reported a low response to a combined test. This led us to hypothesize that PWS patients present at a young age a hypothalamic defect but a normal pituitary function that gradually declines with age. Furthermore, the combined test does not seem to be a useful tool in diagnosing GHD in very young PWS children.

TWO YEAR OF GROWTH HORMONE THERAPY IMPROVES BODY COMPOSITION IN ADULTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Prader-Willi syndrome (PWS) presents clinically with a multitude of findings, including abnormal body composition and partial growth hormone (GH) deficiency. Until now three studies have reported beneficial effects upon body composition of GH treatment in adults with PWS. However, only one of these studies had the optimal randomised controlled design.
AIM: The aim of this study was to confirm and substantiate the results from previous studies.
PATIENTS AND METHODS: 46 patients, 25 women, 21 men, age 29 years (16-41) (median and range) with genetically verified PWS participated in a multinational Scandinavian study. The patients were randomised to treatment with GH (0.6 – 0.8 mg daily) (Norditropin SimpleXx®) or placebo for 12 months, the following 12 months all patients were treated with GH according to their IGF-I value. Body composition was measured yearly by dual x-ray absorptiometry. The study was approved by the local Ethical Committees.
RESULTS: Body fat changed -2.05 vs. +2.60 kg ($P<0.001$) and lean body mass +2.39 vs. -0.00 kg ($P=0.006$) the first year. During the second year non significant changes was found in body fat +0.70 kg ($P=0.37$) and lean body mass 1.10 kg ($P=0.15$) in the group primarily randomised to GH, whereas the change in body fat was -4.51 kg ($P<0.001$) and lean body mass +2.15 kg ($P<0.001$) in the group primarily randomised to placebo.
CONCLUSION: In this first large scale, long-term placebo-controlled study the improvement in body composition by GH treatment in adults with PWS was confirmed. No side effects were observed. Based on our two years results, findings persist during long-term therapy.

EXENATIDE (BYETTA®) INCREASES POSTPRANDIAL FULLNESS WITHOUT SIDE EFFECTS IN PRADER-WILLI SYNDROME - A PILOT STUDY.

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INTRODUCTION: Prader-Willi syndrome (PWS) is associated with hyperphagia and obesity, the major burdens in management of this complex disease. Pharmacological interventions have been disappointing so far, and behavioural constraints are still the only options today. Exenatide (Byetta®) is a drug recently developed for the treatment of type 2 diabetes, and it has been demonstrated to have beneficial effects on appetite suppression and weight loss, but it also has significant side effects which limit its use. To our knowledge, Byetta has not been tested as a suitable intervention against hyperphagia and obesity in PWS. Therefore, we conducted a pilot study to investigate the safety and effectiveness of Byetta on appetite regulation, glucose homeostasis and appetite hormones in PWS and obese controls subjects.
METHODS: We recruited 8 subjects with PWS and 8 obese controls matched for age, sex and body fatness for 2 standardised meal studies at least 2 weeks apart. Subjects received either Byetta 10 ug sc or placebo (normal saline) injected subcutaneously 15 min before start of the meal in a single blinded cross-over design. Glucose, insulin, PYY, GLP-1 and ghrelin were measured for 4 hours postprandially. Appetite and fullness were assessed by a visual analogue scale. Body composition was assessed by Dual Energy X-ray Absorptiometry.
RESULTS: PWS and obese control subjects were well matched for central and total body fat. Fasting glucose and insulin levels, as well as the degree of insulin resistance assessed by homeostasis model assessment, were similar in both groups. Byetta was well tolerated, with no side effects observed in PWS subjects, in contrast to the marked side effects in obese subjects (bloating 75%, nausea 63%, vomiting 25%), consistent with previous reports. Byetta significantly increased fullness, but did not reduce appetite, in both groups. Glucose and insulin levels were lowered similarly in both groups. Furthermore, GLP-1 and PYY levels were suppressed to a similar degree. Ghrelin levels were not affected by Byetta.
CONCLUSIONS: This is the first report on the use of Byetta in PWS, demonstrating that this drug is well tolerated in these subjects, and also similarly effective in increasing fullness and lowering glucose as in obese subjects. Our observation of suppressed insulin levels and unchanged ghrelin levels challenge previous reports and hypotheses on the mode of action of this drug, suggesting delayed gastric emptying might be an important mechanism which should be assessed in future studies. Larger prospective studies should follow to investigate whether chronic administration of Byetta will lead to decreased food intake and weight loss in PWS.

METABOLIC SYNDROME AMONG ADULTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Patients with Prader-Willi syndrome (PWS) die prematurely from complications conventionally related to obesity, including type 2 diabetes mellitus (DMT2), arterial hypertension, respiratory insufficiency and cardiovascular disease (CVD). The etiology of the increased mortality seen in PWS is not completely known. In this context, the metabolic syndrome (MS) is a strong risk factor for atherosclerotic CVD and DMT2, and MS might be one of the mechanisms responsible for excessive mortality in PWS. The metabolic profile of PWS patients, however, is usually more favorable than that in simple obese subjects. Despite marked fat accumulation, the identification of an atypically reduced visceral fat depot in obese PWS females has been advocated to explain a healthier lipid profile and higher insulin sensitivity, compared with matched obese populations. Nevertheless, data on fatness patterning in PWS are still conflicting. In addition, it has been previously demonstrated that several cardiovascular risk factors are already present in pre-pubertal children with PWS. Moreover, obese children and adolescents with PWS showed the same MS prevalence as obese controls (Brambilla et al, Nutr Metab Cardiovasc Dis 2009). In this respect, no data are currently available on the epidemiology of MS in PWS adults. In this study we have estimated the prevalence of MS in a large group of PWS subjects>18 years.
METHODS: Ninety-six subjects with genetically confirmed PWS, 41 males and 55 females, aged 18.1-43.2 yr (mean±SE: 27±0.67), were studied. Anthropometric evaluation included height, weight, BMI (kg/m^2) and waist circumference. Blood pressure (BP) was measured in the supine position. Biochemical testing included measurements of fasting glucose, triglycerides and HDL cholesterol levels. In addition, a standard OGTT was performed in 58 patients, while HOMA-IR was determined in 80 subjects. MS was defined according to the International Diabetes Federation criteria (Diabetic Medicine 23:469-480, 2006).
RESULTS: 29 subjects had no more than 1 abnormality of the MS, whereas 69.8% of patients had 2 or more. The overall prevalence of the MS was 41.7%, affecting 23 females (41.8%) and 17 males (41.5%). The distribution of each element of the MS was the following: visceral obesity 93.7%, elevated BP 48.9%, IGT/DMT2 38.5%, low HDL 34.4%, high triglycerides 16.7%. Three patients had hyperinsulinemia (3.7%), and 31 subjects (38.7%) showed insulin resistance (HOMA-IR>2.77).
DISCUSSION: The frequency of MS was lower in our PWS patients than those reported in simple obesity (Park et al, Arch Intern Med 2003). This finding is probably due to the reduced prevalence of insulin resistance. However, our results demonstrate that MS affects a significant percentage of young PWS adults, suggesting a relationship with the increased cardiovascular morbidity and mortality. These data point to the importance of early therapy of all CVD risk factors associated with PWS in late adolescence and during adulthood.

HYPOGONADISM IN PRADER-WILLI SYNDROME: A SPECTRUM FROM PRIMARY GONADAL TO PRIMARY HYPOTHALAMIC DYSFUNCTION

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INTRODUCTION: Although many features of Prader-Willi syndrome (PWS) have been attributed to hypothalamic dysfunction, recent studies (1,2) have shown that a primary gonadal defect plays a major role in to the etiology of the hypogonadism. PWS individuals appear to have a unique defect in gonadal function characterized by normal anti-Müllerian hormone (AMH) levels but markedly low or undetectable inhibin B levels.
METHODS: We measured reproductive hormones on a cross-section population of 35 adolescents and adults with genetically confirmed PWS. Puberty was assessed by Tanner staging and a blood sample was taken from 17 males and 18 females ages 11 to 32 years.
RESULTS: We defined four groups of PWS individuals according to the relative contributions of primary gonadal defects vs hypothalamic dysfunction. Group A - primary hypogonadism - consisted of 8 subjects (7 males) with elevated FSH levels (> 20 IU/l) and undetectable inhibin B (<7 pg/ml). In group B, hypothalamic hypogonadism was seen in 7 individuals (3 males) with FSH < 0.5 IU/l and inhibin B < 7 pg/ml. Group C consisted of 8 patients (3 males) with evidence of partial gonadal and hypothalamic function with inhibin B > 20 pg/ml and FSH in the 2 to 10 IU/l range. Group D had 12 patients (4 males) with mild hypothalamic and severe gonadal dysfunction (FSH 0.5-10 IU/L and INB < 20 pg/ml). Ages (mean±SD) were similar in each group: 23.4±6.1, 20.4±6.7, 22.2±5.0, 19.9±5.4 years for groups A, B, C, and D.
In males, FSH and LH levels were 33.5±10.6, 0.2±0.0, 4.8±2.8, and 8.4±6.2 and 5.9±4.4, 0.1±0.1, 3.4±1.0, and 2.0±1.5 IU/l for groups A, B, C and D, respectively. Inhibin B levels were undetectable, 10.6±4.0, 73.1±9.7, and 8.5±1.7 pg/ml and AMH levels were 2.3±2.3, 17.0±15.8, 3.0±1.5, and 4.6±4.2 ng/ml in groups A, B, C, and D. Testosterone levels were 1.9±0.8, 0.4±0.1, 2.6±1.4, and 0.9±0.3 ng/ml.
In females, FSH and LH levels were 24.7, 0.4±0.1, 7.0±2.7, and 5.3±3.5 and 5.8, 0.1±0.1, 4.2±2.4, and 1.7±2.3 IU/l in each respective group. Inhibin B was undetectable in female groups A and B and 34.7±15.4 and 8.6±1.4 pg/ml in groups C and D. AMH levels were <0.02, 1.0±0.9, 1.1±0.05, and 1.4±0.9 ng/ml. Estradiol levels were 91, 236±232, 134±72, and 103±80 pmol/l.
Genetic diagnoses were group A: 7 deletions (DEL) and 2 uniparental disomy (UPD); group B: 4 DEL, 2 UPD, 1 maternal fragment; group C: 4 DEL and 4 UPD, and group D 7 DEL and 5 UPD.
CONCLUSIONS: The pathophysiology of hypogonadism in PWS is heterogeneous on a spectrum from primary hypogonadal hypogonadism to primary hypothalamic hypogonadism. In most patients, primary gonadal dysfunction is the major cause of hypogonadism, while severe, isolated gonadotropin deficiency is less frequent.
REFERENCES: (1) Hirsch et al, JCEM, 2009;94:2262 (2) Eldar-Geva et al, Eur J Endocrinol, 2010;162:377

TESTOSTERONE REPLACEMENT THERAPY IN 18 ADULT PATIENTS WITH PRADER-WILLI SYNDROME

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BACKGROUND: All males with PWS show various degrees of hypogonadism and it causes decrease of bone and muscle mass. However, testosterone replacement therapy has been controversial due to anecdotal concerns that testosterone might cause inappropriately aggressive behavior or worsen other behavioral problems.
PURPOSES: To evaluate the effect of testosterone on behavioral problems, muscle volume, bone mineral density (BMD), body composition, and body mass index (BMI) in PWS.
SUBJECTS & METHODS: Eighteen male patients (age ranging from 16 to 54 years, chromosome 15q deletion in all 18 pts, duration of therapy 1.0 to 12.8 years, mean 4.6 years) who have been treated with testosterone (125 mg depot testosterone i.m. once monthly) were evaluated for the following issues; behavior (monthly examination and interview from the patients and their parents), paravertebral muscle volume (CT scan), BMD of lumbar spine (DEXA), lean body mass (DEXA), %fat at the trunk area (DEXA), and BMI. Data analysis was conducted using paired t-test. P value below 0.05 was considered significant.
RESULTS: None of the patients showed worsening of behavioral problems and 6 patients showed improvement of their irritability. All of them increased skin pigmentation and beard, increasing their self confidence. Eight of them had erection of penis and one experienced sperm ejection about once monthly. Paravertebral muscle volume did not change statistically. BMD and lean body mass increased significantly ($p<0.005$). %fat and BMI did not change during the treatment.
DISCUSSION: Testosterone replacement therapy did not worsen behavioral problems and rather improved aggressive behavior in some patients. Self-confidence increased in all. %fat and BMI did not improve but BMD and lean body mass increased.
CONCLUSION: Testosterone replacement therapy in male adults with PWS is a safe and useful treatment.

INVITED SPEAKER:

CONVERSION OF BRAIN CYTOSOL PROFILE FROM FETAL TO ADULT TYPE TAURINE-NAA EXCHANGE

Tsutomu Nakada

Council Member, Science Council of Japan

Mammals face drastic environmental changes at birth. Appropriate adjustments of various systems must take place rapidly to accommodate this once in a life time event. The perinatal adjustment processes of the circulatory and respiratory systems are well known examples. The adjustment processes the central nervous system (CNS), on the other hand, had been under recognized. The brain undergoes significant adjustments post-natally, the most obvious of which is its need to meet the drastic increase in energy consumption at the neuronal cell membrane due to the explosive increase in neural activities after birth. Using various advanced magnetic resonance spectroscopy (MRS) techniques, we identified that changes in the cytosolic microenvironment play a key role in post-natal adjustment. Taurine, a free cytosolic amino acid rich in fetal brain is central in the fetal type of acid-base balance control system (taurine buffer). Taurine also, however, retards cytosolic high energy phosphate (HEP) transport. In early post-natal life, taurine is rapidly replaced by another cytosolic free amino acid, N-acetyl-aspartate (NAA) to facilitate HEP transport

BRAIN DEVELOPMENTAL DIFFERENCES IN PRADER-WILLI SYNDROME DETECTED BY DIFFUSION TENSOR IMAGING

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INTRODUCTION: While the developmental and behavioral aspects of Prader-Willi syndrome (PWS) have been characterized in detail and conventional neuroimaging studies have identified its macrostructural features, the specific cerebral developmental differences underlying the clinical features remain to be elucidated. Diffusion tensor imaging (DTI) is a non-invasive imaging technique capable of providing quantitative indices of brain development and is a suitable technique for detecting diffusion characteristics changes in PWS. The aim of this study was to detect regional differences associated with brain development in PWS using DTI based on a high-field MR system.
METHODS: DTI studies were performed on a 3.0 Tesla MR system in 15 individuals with the diagnosis of PWS (age range 11-41 years, 10 males, 5 females, all of deletion type) and 15 age and gender matched control subjects. Diffusion characteristics were assessed simultaneously in multiple representative brain regions, deep gray matter (caudate head, putamen, and dorsomedial thalamus) and white matter structures (frontal and parietal white matter, posterior limb of the internal capsule, and corpus callosum). The former was analyzed by trace value (Tr), averaged values of diffusivity without directional consideration, and the latter by fractional anisotropy (FA), an index that provides information of deviation (anisotropism) associated with neural fiber integrity or connectivity.
RESULTS: In individuals with PWS, Tr was found to be significantly higher in the left caudate head and left dorsomedial thalamus, whereas FA was significantly reduced in both the frontal white matter and posterior limb of the internal capsule bilaterally, and splenium of the corpus callosum. The observed diffusion characteristics indicate developmental differences in these regions and provide anatomic substrates consistent with the clinical features of PWS.
CONCLUSIONS: The study provides objective evidence that individuals who have PWS indeed have developmental differences in specific areas of the brain. The findings provide not only new insights into developmental pathophysiology, but also an opportunity for interventional strategies for the behavioral issues in PWS.

HYPOTONIA IN NEONATES WITH PRADER-WILLI SYNDROME IS NOT ALWAYS SEEN AT BIRTH BUT BECOMES EVIDENT AFTER THE FIRST DAYS

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INTRODUCTION: Neonatal hypotonia is a main feature of Prader-Willi syndrome (PWS). The cause is unknown. Anecdotally is reported that hypotonia is not always observed at birth but a few days later together with feeding problems.
METHODS: Neonatal data of 10 patients with genetically confirmed PWS were studied (15q deletion (5), maternal disomy (4), 15q imprinting mutation (1)). Gestational age, weight, Apgar score and clinical symptoms were recorded.
RESULTS: 2 were delivered prematurely (33 and 34 weeks) for medical reasons. 6 had low birth weight for gestational age. 9 had normal Apgar scores, one premature girl had Apgar 9/10 because of hypotonia. During the first hours after birth only one was admitted to the neonatal department for hypotonia, 4 were admitted for other reasons (prematurity, aspiration, mild respiratory distress) and in these hypotonia was first seen after 1-3 days. 5 were admitted for hypotonia and feeding problems at ages 1-7 days, described also as being increasingly quiet and sleepy. Facial dysmorphology was noted in 7. All boys (3) had cryptorchism. None had hypoglycemia.
DISCUSSION: Hypotonia and other typical symptoms in neonates with PWS are not always observed at birth but most often during the first days. A normal Apgar score includes normal muscle tone. Cases with both low and normal Apgar scores in PWS have been published previously. Our data call attention to a possible clinical change during the first days. One question to be considered is if any normal neuronal or hormonal stimuli gradually disappear. When the diagnosis is known or suspected it is of interest to measure blood levels of various hormones, for example melatonin and cortisol.

INVITED SPEAKER:

PRADER WILLI SYNDROME: GENE EXPRESSION AND PREMATURE ALZHEIMER DISEASE

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In the past 25 years, the brains of 16 individuals with Prader-Willi syndrome (PWS) were donated for research from Belgium, Denmark, France, The Netherlands, New Zealand, Switzerland, UK and the USA. They were matched to brain samples from our own collection of >2000 brains as controls for studies of 2 major questions: 1) where are the genes of the PWS region expressed in controls, what may be the relationship to the PWS symptoms and what is the difference in PWS brains, and 2) is there any evidence for a premature occurrence of Alzheimer disease in PWS?

EXPRESSION OF PWS REGION GENES

PWS is thought to result from the loss of paternal contributions for a 2-Mb imprinted region on the proximal long arm of human chromosome 15. Up to now, five paternally active genes have been identified in this region (*ZNF127*, *Necdin*, *MAGEL2*, *C15orf2*, and *SNURF-SNRPN*). In addition, more than 70C/D box snoRNA genes have been mapped to this region, one of which is the SNORD16 (HBII-85) cluster.

Surprisingly we found expression of *NDN* and *C15orf2* genes on the mRNA and protein level in hypothalamic nuclei of PWS patients, such as the Paraventricular Nucleus (PVN), and Supra Optic Nucleus (SON) in both uniparental disomy and deletion patients. Expression of *NDN* and *C15orf2* also occurred in the cortex of PWS patients. The youngest PWS sample was from a 6-month old patient. The results so far contradict the classic assumption that in case of imprinting in PWS the maternal allele is silenced in the brain. These findings suggest that there may be leaky expression from the maternal allele, cell-type specific imprinting in postnatal brains, or that a loss of imprinting has occurred, at least in a fraction of cells. These findings seem to exclude these genes as major candidates for the symptoms of PWS, but an effect of a lack of expression of these genes during foetal brain development can not be excluded at present.

The results of a study on the expression of snoRNA HBII-85 in the nucleoli of the hypothalamic cells using a new in situ hybridization technique will be discussed.

PREMATURE OCCURRENCE OF ALZHEIMER DISEASE (AD) IN PWS

Only recently people with PWS are becoming older than 40 years of age. Anecdotal information about premature aging and dementia is now reaching us via PWS societies, parents and caregivers. Using immunocytochemical staining of hyper-phosphorylated tau (AT8) and a Bodian silver staining, we found indeed evidence for a premature occurrence of typical AD changes. Neurofibrillary changes staining for hyper-phosphorylated tau were found in the neocortex of all 3 PWS patients of 49, 51 and 64 years of age. In the

hypothalamus, we found pronounced early AD changes, especially in the PVN that has a clearly diminished cell number in PWS. Our findings are interesting since the PVN is apparently a vulnerable structure in PWS and is instrumental in a number of symptoms in PWS. Now that more persons with PWS are surviving longer, it seems that we find premature aging and dementia, probably of the AD type, as a new challenge.

It now becomes, therefore, urgent to study the clinical manifestations, neuropathology and the possible risk factors of dementia in PWS, such as diabetes, hypercholesterolemia and the lack of sex hormones and also the possible positive effects of growth hormone treatment. In a wider perspective, our study points to an important health problem: Obese patients might be prone to early-onset AD.

INVITED SPEAKER:

PSYCHIATRIC AND BEHAVIOURAL ISSUES IN PRADER WILLI SYNDROME

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Prader Willi Syndrome (PWS) is typically associated with a range of behavioural and emotional disturbances. These develop early in childhood and peak in late adolescence and early adulthood. There is some evidence that they decline in middle adulthood. The behaviours span a number of different domains. Some behaviours reflect an emotional maturation which is delayed compared with intellectual maturation. Impulsiveness and aggression are features of the rages that are a source of distress. Obsessive behaviours have been studied, with perseveration and preoccupation a feature. Another domain is sensory related, including behaviours such as skin-picking, and altered pain and temperature sensation. Alterations in sleep and alertness are also a feature.

In late adolescence, a vulnerability to episodes of psychotic disturbance is apparent, particularly, but not exclusively, in those with uniparental disomy. Less appreciated is that depressive illness may be more common. Data on cognitive functioning will also be reviewed.

These emotional and behavioural difficulties will be discussed at several levels. First, the epidemiology of the psychiatric and behavioural problems, and its uniqueness compared with other developmental disabilities. Second, the relationship between the behaviours and the pathophysiology of PWS, particularly in connection with evidence for hypothalamic dysfunction. Third, the impact of behavioural problems on the adaptive function of the PWS individuals, and its relevance for families and the community. Fourth, we will review the evidence for the impact of therapies on the behavioural disturbances. The potential for intervention with oxytocin administration will be discussed.

AN EXAMINATION OF THE UNDERPINNINGS OF A MULTI-LEVEL STRATEGY FOR ADDRESSING THE PROBLEM OF TEMPER OUTBURSTS IN INDIVIDUALS WITH PWS AND AN INITIAL EVALUATION OF THIS STRATEGY

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INTRODUCTION: Temper outbursts comprise part of the behavioural phenotype associated with Prader-Willi syndrome (PWS). These temper outbursts can be associated with a preference for routine/predictability which may be linked to a specific cognitive deficit in attention switching.
METHODS I: fMRI was employed to assess whether individuals with PWS show brain functional abnormalities that may underpin a deficit in attention switching. Eight individuals with PWS (and 8 controls) were imaged during a switching paradigm. To assess whether a pathway between a specific deficit in attention switching and temper outburst behaviour can exist in individuals with PWS, a series of single-case experiments was carried out. These experiments used environmental manipulation, behavioural observation and physiological recording to assess the effect of placing a purely cognitive demand on individuals' attention switching abilities and unexpectedly changing individuals' routines/expectations.
RESULTS I: Individuals with PWS showed dysfunction in prefrontal, anterior cingulate and parietal brain regions that was associated with abnormalities in attention switching. Results suggested that the specific deficit in attention switching in individuals with PWS can lead to temper outburst behaviour. Unexpected changes in the environment appear to place a demand on individuals' attention switching ability, which can trigger low-level temper outburst related behaviour or full temper outbursts.
CONCLUSIONS I: It may be possible to improve temper outbursts by intervening at both cognitive and environmental levels.
METHODS II: The efficacy of three potential intervention strategies for reducing temper outburst behaviours will be evaluated using behavioural observation and physiological recording in tightly controlled experiments. Physiologically validated parental report will also be employed as an evaluation tool. 1) Twenty individuals with PWS will take part in a computer based attention switching training programme administered over the course of fifteen months in a multiple baseline, placebo controlled design. 2) A cueing strategy will be administered aiming to increase the predictability of changes. 3) Individuals' reactions to unexpected changes will be investigated in order to determine whether the level of exposure to a particular routine/expectation without change is a critical factor affecting a person's behavioural reaction to an unexpected change, information that would be important when advising parents on how best to structure a person with PWS' environment.
RESULTS II: Preliminary results address the third potential intervention strategy. Five novel activities were administered to participants for varying amounts of time before unexpected changes to the routines/expectations that had been established during the game were introduced. The behavioural and physiological reaction of individuals to the unexpected changes following each of the five activities will be presented.
CONCLUSIONS II: It is possible that an early intervention strategy that encourages carers of people with PWS not to allow routines to become established may be beneficial in helping to minimise future temper outburst related behaviour.

VOLUNTARY FASTING IN ADOLESCENTS AND ADULTS WITH PRADER-WILLI SYNDROME.

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INTRODUCTION: Yom Kippur is a religious holiday, a day of self-reckoning during which healthy persons, above the age of 12-13 years, are required to fast for 25 hours. More than 60% of the Jews in Israel, including many secular persons, respect the holiday and participate in the fast. We have observed voluntary fasting among our adolescent and adult patients with PWS, who otherwise eat compulsively and transgress any civil or religious rule to obtain food. It was our goal to study this paradoxical behavior in a prospective survey. We hypothesized that genotype, eating habits, control patterns, motivational attitudes and religiosity would correlate with ability to fast.
METHODS: The study group consisted of the 31 Jewish patients in Israel with PWS, above the age of 12 (girls) and 13 (boys) years that live in a residential home or at a home where at least one close relative or resident fast. We obtained data from 27 patients (14 males and 13 females), age 12-34 (mean age 21.9±6.1 years). Demographic, clinical, behavioral and cognitive data were collected from the patients and their caregivers through structured interviews and questionnaires before the fast. Among other tools, we used the Three Factors Eating Questionnaire – revised 18 (TFEQ-R18), and an unpublished questionnaire in use in our multidisciplinary clinic tapping demographic and clinical data about age, gender, genotype (UPD, deletion), level of religiosity, profile of PWS behavioral characteristics, control perception and motivational attitudes. Data collected from caregivers following the fast was whether the person actually tried to fast, length of the fast and if the fast was indeed completed.
RESULTS: To our surprise most of the individuals who decided to fast were able to complete the fast. Specifically, of the 27 cases collected, one did not show any intention or strive to fast, 6 expressed intention to fast but did not accomplish the wish, 3 fasted most of the day, and 17 completed the fast. The fasting group (patients who fasted all or most of the day, n=20) and the non-fasting group (patients who intended to fast but did not fast, n=6) were compared on demographic, clinical and behavioral measures. No significant differences between groups were found regarding most of the measures, including age, gender, dwelling, genotype and religiosity. However, the fasting group reported lower uncontrolled eating on the TFEQ-R18 ($p<.05$).
CONCLUSION: Our findings indicate that most of the adolescents and adults with PWS can participate in a religious fast. Contrary to our expectations, this ability was not accounted for by demographic and clinical variables such as age, gender, genotype and religiosity. On the other hand, level of uncontrolled eating seems to play an important role in this fasting ability.

RECENT MORTALITY RATES AND RISK OF DEMENTIA IN PWS

Joyce Whittington, Tony Holland

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INTRODUCTION: The effects of ageing in people with Prader-Willi syndrome (PWS) has generated little research because of the high mortality rate and the fact that there are very few people with PWS surviving to age 40, 50, or beyond. Based on the age structure of a population sample of people with PWS, the mortality rate in 2001 was estimated to be about 3% per annum. At a meeting of the European PWS research group in 2007, Swaab reported on the pathological findings in the brains of three older people with PWS aged between 40 and 60 years at death. Alzheimer-like plaques and tangles increasing with age were observed in the brains. This raised the possibility of the risk of early-onset dementia in people with PWS. We address two specific questions relating to ageing: Has the mortality rate decreased since 2001? Is there any evidence of dementia in people with PWS surviving over age 40?
METHODS: (1) An attempt was made to trace all the participants from the population study by writing to, or telephoning, parents or carers at their last known address. If this failed, an attempt to trace them was made through the PWSA-UK. Some deaths were notified directly to our research group and some through the PWSA-UK or other contacts.
(2) All people with PWS aged 40 or over were contacted through the PWSA-UK and they and their parents/careers were invited to participate in a study of possible symptoms of dementia. Parents/carers were interviewed using the CAMDEX informant interview and DSQIID questionnaire – both designed to identify symptoms of dementia in people with ID.
RESULTS: Fifty-one out of 62 from the previous population cohort (1998-2000) were traced, 7 of whom were found to have died (mortality rate of 1.5% p.a.). If it is assumed that all untraced were still alive the mortality rate was 7/62 over 9 years (1.3%). To assess the risk of dementia, 26 out of a possible 43 people with PWS aged 40+ identified were recruited. Twenty two showed no dementia, one mild/moderate dementia, one probable mild dementia and one had evidence of age-related cognitive decline. In one other person there had been decline but the diagnosis was difficult because of a current psychotic episode. The three affected were female, of maternal UPD genetic subtype, or had a disomic region, and all had a long history of psychotic illness.
DISCUSSION: The research presented here is very preliminary; clearly, a much larger sample is required. On the other hand, informants were either parents or carers who had known the participants well for many years and had observed changes over and above the episodes of psychiatric illness. In the general population people with bipolar disorder may be at risk for more rapid cognitive decline, but when they get dementia it tends to be in later life. Our sub-group of people with PWS described above may be at risk of early onset dementia.

PWSA (USA) FAMILY REPORTED MEDICAL QUESTIONNAIRE RESULTS

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INTRODUCTION: In order to further characterize the long term medical outcome and natural course of Prader-Willi syndrome (PWS), Prader-Willi Syndrome Association (USA) designed and conducted a medical survey in 2004. 1,787 subjects responded to the first survey, with age range from infancy to 67. The 2nd medical survey includes another 520 individuals with PWS. The data from the two surveys will be reported. Because the amount of information obtained is extensive, selective aspects will be presented. A written summary of all collected information will be distributed at the conference.

METHODS: The PWSA (USA) conducted two large-scale questionnaire surveys of families who have a child or adult with PWS, which enables documentation of ongoing medical issues. Collected data was stratified and analyzed by: age, prenatal history, molecular mechanism, BMI, with and without growth hormone treatment, behavior phenotype including skin picking, autistic behaviors, and food preoccupation, seeking/looking vs. locking, medical complications of all organ systems, living arrangement, educational preferences, and use of alternative medications.

RESULTS: Survey #1 include 1,787 subject with female: male = 52: 48. Of those, 777 with sleep apnea (43%), 358 with other respiratory complications (20%), 592 curvature of the spine (33%), 203 with GI problems (11%), 187 diabetes (10%), 171 with heart problems (10%), 165 with hypothyroidism (9%), 159 with osteoporosis (9%), 247 with fractures (14%), 130 with hip dysplasia (7%), 61 with gallbladder disease (3%), 617 with severe skin picking (34.5%), 199 with seizures (11%), 246 with autistic type behaviors (14%), 630 with strabismus (35%), 262 with pubic or axillary hair before age 8 (15%). Of note, in age 3-18 group, based on the reported BMI, those who received growth hormone therapy (GHT), 75% percent are of normal weight, 12% overweight and 11% obese; without GHT, 40 % are obese, 15% overweight. Regarding births, 418 were breech (23%), 439 premature (25%), 503 emergency c-section (28%), and 937 tube fed (52%). Survey #2 is still being analyzed, but will be completed by the conference. Note that these statistics are fluid since new and revised entries are received daily.

DISCUSSION: We recognize that survey based data collection has limitations for medical research. The respondents were a self-selected group motivated to cooperate with research on their children's condition. Ascertainment bias may exist but may also be overcome by a large sample as collected here. An additional drawback was the lack of confirmed molecular diagnosis in some patients. The strength of the study is its large sample size, its ascertainment of a broad age range and its detailed coverage of many relevant issues of interest. Despite some limitations, our data serve as a good resource for caretakers/providers and as a protocol to enable research in rare diseases.

IN SUMMARY: The medical issues of PWS are extensive and complex. Our goal is to highlight areas of need and key issues with PWS and share with families and people who know and care the most. The study also demonstrates the possibility of using survey based methods to study rare diseases for its natural course and characterize the medical complications, long term outcome and benefits and side effects of current treatment.

ENDOCRINE DISORDERS IN CHILDREN WITH PRADER-WILLI SYNDROME - DATA FROM 226 CHILDREN AND ADOLESCENTS OF THE FRENCH DATABASE

G. Diene, E. Mimoun, C. Molinas, M. Tauber

On behalf of the French Reference Centre for PWS

Centre de Référence du syndrome de Prader-Willi, Division of Endocrinology, Genetics, Gynaecology and Bone Diseases, Hôpital des Enfants, Toulouse, France

INTRODUCTION: The French reference centre for Prader-Willi syndrome was set-up by the health ministry in November 2004. One of the objectives of the centre is to set-up a database starting with children and adolescents containing medical and psychosocial data. This database is partially supported by Pfizer Inc.
POPULATION: Four hundred and seventeen children and adolescents with PWS have been identified all over the country. Two hundred and fifty five patients (61.2%) are already included in the database and inclusions are still ongoing.
RESULTS: Among the 255 included patients (51.5% of boys, median age 7.3 years), 226 have a genetic confirmed diagnosis (88.7%) and 29 were ongoing of confirmation of the clinical diagnosis. Genetic diagnosis was made at a median age of 2 months [0.05 - 196 months]: 58% had a deletion in chromosome 15q11-q13, 29% uniparental disomy, 1% translocation involving the PWS region, 2% imprinting defect, and 10% abnormal methylation profile.
Median BMI Z-score was +1.3 for a median age of 7.3 years, 17.8% of patients presented overweight and 21.5% presented obesity (International Obesity Task Force 2000 criteria). Growth hormone deficiency was present in 82% of patients and 85% were treated, with a height gain of +1 SD and a BMI reduction of -0.6 Z-score achieved in the first year of treatment. Hypogonadism was present in 46% patients, and hypothyroidism in 30%. Glucose intolerance was found in 4% of patients, but no diabetes mellitus was detected in the 74 patients explored.
CONCLUSION: Our report gives an overview of endocrine dysfunctions recorded in a large registry database of French children and adolescents with PWS. A same database will be started soon for adult patients older than 18 years.

SETTING UP A NATIONAL DATABASE TO CAPTURE BASELINE AND FOLLOW UP DATA OF CHILDREN WITH PWS ON GH IN AUSTRALIA AND NEW ZEALAND 2009/10

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INTRODUCTION: For many years there has been a need for a database to be set up in Australia and New Zealand for children with Prader-Willi syndrome (PWS) for several reasons. Currently, we still have no reliable source of the total number of children or adults with PWS in Australia. Patients attend a variety of clinics and private practices. Therefore, the number of patients in each clinic is often not large enough for research. Because there exists a wide variation in the characteristics of individuals with PWS due to the different expression of PWS in people with deletion, disomy or imprinting defects, we need substantial numbers to reach meaningful outcomes in research.
The Australia-New Zealand PWS database will address a number of important questions. Primarily, the PWS database will provide information on benefits and side effects of the GH treatment and will assist in improving the guidelines of management of children with PWS by long-term monitoring of children on the GH treatment. Presently we are analysing the baseline data of children starting on GH via the GH program for PWS and we look forward to present these.
Ultimately the database will be a reliable source of information to substantiate the request for continuation of GH treatment in adults.
METHODS: 1) Identification of multidisciplinary and other hospital based clinics with children with PWS around Australia. 2) Setting up a collaboration among all contributing clinicians of each hospital. 3) Agreement on characteristics to be entered in the database, the suggested protocol and agreement on tests. 4) Ethics proposals to all hospitals. 5) Obtaining baseline and follow up data. 6) Analysis. 7) Reporting
RESULTS: Eight major clinics with children with PWS were identified in Australia and one in New Zealand. Collaboration was established via the Australasian Paediatric Endocrine Group (APEG) with the PWS subgroup members to support the database. Ethics approvals have been obtained. Presently additional clinics in Australia and New Zealand will be incorporated in the database.
Great differences exist in the running of the clinics and also in the test results among hospital clinics. This is due to differences between hospital and patient preferences. Hence communication and coordination is essential and stream lining of test procedures and equipment is advised. We will discuss some of these in the presentation in addition to the baseline data on patients at start of the GH program.
CONCLUSION: It has been a great step forward to having a number of hospitals in different states and countries collaborating on research on PWS. The response has been very positive. There have been a number of suggestions of entering additional data and these will be considered. Thus the database may be expanded to also cater to other aspects in future.

THE EUROPEAN PRADER-WILLI SYNDROME DATABASE: A TOOL TO SUPPORT RESEARCH INTO A RARE SYNDROME

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INTRODUCTION: An internet-based Prader Willi syndrome (PWS) specific database has been established, with support from Framework 6 of the Life Sciences, Genomics, and Biotechnology for Health Programme of the European Union. The Database has been designed to be used as a tool to support multi-site and longitudinal studies into what is a rare neurodevelopmental disorder. It is the rarity of the syndrome that requires that such multi-national studies are possible so that sufficient numbers of participants can be identified, whether for clinical trials or for studies which are exploring many different variables. In this presentation the administration and use of the database will be considered.
METHODS: An expert multidisciplinary group including clinicians involved in PWS research and in clinical practice, together with expert software developers and representatives from two national PWS Associations agreed on the content and structure of the database and undertook preliminary trials of its use. The same group also agreed on the administrative structure for the database and the conditions for its use and prepared an accompanying manual.
RESULTS: The database is now established, with over 1200 fields organized in a branching structure that can be entered through six 'index' entry points, and subsequent panels and sub-panels. In addition to having to agree on the clinical assessments and subsequent fields to be included in the database, the issues of concern were those relating to confidentiality, sharing of data, and publications. A problem now is the possibility of obtaining funds to support research across national boundaries and for modifications to the database as and when necessary.
CONCLUSIONS: The case for such a database is very strong, particularly given the rarity of PWS and the need that similar instruments must be used for the collection of data if data is to be combined across sites and/or compared over time. The main challenges for the future include developing national structures to support and protect data in each participating country over many years, obtaining funding to undertake collaborative research, and establishing a robust management strategy.

ABSTRACTS OF POSTER PRESENTATIONS

1. 11 YEARS OF TREATMENT OF CHILDREN AT THE CENTRE FOR CHILDREN WITH PWS IN HILDESHEIM: RESULTS AND PROBLEMS

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INTRODUCTION: PWS is a complex neurogenetic disorder. The hyperphagia and the behavioural problems stress the families' life. Our treatment strategy comprises dietary management, physical activation and exercises, hormonal treatment, and behavioural consultation. Parents get special training to put into practice
METHODS: Data from the patients' records were analysed retrospectively. 80 PWS preschool and school children (41 boys and 39 girls), aged from 4.6 to 19.3 years (mean age 10.7.years) were included.
The children presented at a mean age of 5.17 years, the oldest being 12.3 years; one child was born in our clinic. Children came for the consultations from all over Germany, usually four times in the first year of treatment. Later they are treated at our centre twice a year. The mean treatment period was 5.56 years (range from 0.6 years to 10.8 years).
RESULTS: 81.25 % of the children with PWS had normal weight, 17.5% of the children were obese, and one girl was underweight. The BMI-SDS ranges between 2.7 to 3.8 (mean BMI-SDS 0.79). The obese children had a mean age of 13.8 years compared to 9.95 years in normal weight children with PWS.
70 children were treated with GH. The GH therapy was started at mean age of 5.3 years (0.94 to 12.37 years). 51% of the families lock the kitchen. Their children are older and behavioural problems were reported more often by their parents. The mean BMI-SDS of these PWS children was higher than in the other group. There was no difference between boys and girls. Behavioural problems were reported more often in children who attend schools for children with special needs.
19% of the children attended a regular school. Their mean BMI-SDS was higher than the BMI-SDS of the pupil in the schools for children with special needs. They showed less behavioural problems.
DISCUSSION: GH treatment changes the life of children with PWS. More often children with PWS attend regular schools as a part of integration concept for children with special needs. In well organised families with a structured diet the children learn to accept their special meals, to ask for additional snacks and to stay away from unlocked food. Consequent weight management is successful in over 80% of the treated children. So, obesity occurs later and less often than usually reported in the literature (Butler, Hanchett, Thompson, 2006). The acceptance of daily exercises after finishing physiotherapeutic programmes is rare.
Behavioural problems and obesity occur more often in older children but significantly less than reported (Dykens, 1996). 30% of the families reported that the temper tantrums stress family life more than the diet management.
Special training is needed for parents and caregivers as well for teachers to deal with the behavioural problems professionally.

2. BENEFITS OF A MULTI-DISCIPLINARY CLINICAL APPROACH TO PRADER-WILLI SYNDROME CHILDREN

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INTRODUCTION: PWS is a rare and complex genetic disorder requiring a wide range of medical and support services for patients and families. The care of such children demands the expertise of many interrelated medical subspecialities and must be appropriate for the developmental age. Regular attendance at clinic allows closer monitoring of growth and development, dietary and psychosocial issues to be addressed while allowing for different speciality areas to be closely involved in the patient's overall care. Hence, we established a multi-disciplinary clinic for care of children with PWS. The aim of this study is to assess the satisfaction of the families and carers of children with PWS.
METHODS: The paediatric multidisciplinary PWS clinic includes Endocrinology, Respiratory, Behavioural, Genetics and Nutrition. There are 54 families from Queensland and Northern New South Wales who attend the clinic, varying in ages from newborn to 18 years. There are 6 clinics a year; 2 for each age appropriate category, i.e., babies, primary school age and high school age. A transitioning to adult services takes place in the high school age group. The clinic is supported by a Co-ordinator and Endocrine Nurse. The Co-ordinator acts as the central communication point for parents and specialists. Blood tests and bone age X-ray are performed annually The PWS Clinic allows for patients and families to see up to 5 specialists in one morning, offering a "one stop shop" and the ability for doctors to consult with each other at the time of the appointment. The Co-ordinator liaises with other speciality areas to have organised appointments. Data collected from each visit is used for research in each specialty area with particular reference to the monitoring of BMI and prevention of obesity in these children.

Table A	Weight SDS (<3 years)		BMI SDS (>3yrs)		HEIGHT SDS	
	Mean	SDS	Mean	SDS	Mean	SDS
Toddlers	-0.63	(1.62)	+1.27	(1.29)	-0.98	(1.74)
Pre School			+1.04	(1.77)	-0.63	(1.33)
High School			+2.38	(1.65)	-2.36	(1.58)

Table B	Insulin (mU/L)		Glucose (mmol/L)		Cholesterol (mmol/L)	
	Mean	SDS	Mean	SDS	Mean	SDS
Toddlers	3.84	(2.35)	4.38	(.053)	4.39	(0.79)
Pre School	9.44	(11.97)	4.65	(0.59)	4.38	(0.70)
High School	13.11	(7.01)	4.66)	(0.83)	4.28	(0.83)

RESULTS: Offering a multidisciplinary clinical approach has been met with a very positive response by families and medical staff. Attendance rates are very good and the clinic provides a familiar and supportive environment for families. Compared to the published data our mean BMI SD for all three groups are considerably lower, with no significant metabolic complications.

3. ORTHOPAEDIC MANIFESTATIONS OF CHILDREN WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Prader Willi syndrome (PWS) is a common genetic cause of obesity. A number of manifestations of PWS lead to development of obesity, for example hyperphagia, somnolence, low energy expenditure and endocrinological disorders such as deficiencies of growth hormone (GH), thyroid stimulating hormone, and hypogonadotrophic hypogonadism. Low muscle tone and orthopaedic conditions in PWS lead to difficulty in physical activity and hence difficulty in treating obesity. While preventative measures of development of obesity in children with PWS are vital, the increase of physical activity is equally important for weight control. Therefore, early recognition and treatment of orthopaedic manifestations in children with PWS is crucial. Similarly, low muscle tone needs to have appropriate medical attention. Few studies have been done to identify the extent of the orthopaedic problems in adults with PWS. No paediatric data is available regarding prevalence of orthopaedic conditions in current PWS literature. Hence we aimed to assess it in children with PWS.
METHODS: We performed a cross-sectional descriptive study on our paediatric PWS cohort. All the patients were diagnosed after genetic testing. They were assessed by a single observer who is a trainee in paediatric orthopaedic surgery (AG). Age, gender, height, weight, GH treatment and history of orthopaedic problems were obtained during consultation. Physical examinations pertaining to orthopaedic conditions were done by AG. To complement the clinical assessments all children had anterior-posterior X-ray of the pelvis and PA X-ray of the thoraco-lumbar spine. Acetabular index and Reimer's migration percentage were used to assess hip dysplasia. Cobb's angle was measured to assess spinal deformity.
RESULTS: 37 children (12 males) were reviewed and the mean age was 7.16 yr (±6.43 yr). BMI SDS was +1.52 (±1.16), weight SDS was +0.09 (±1.62) and height SDS, -1.23 (±1.72). 30.6% of the cohort was on GH therapy. Planovalgus feet was noted in 26 (70.2%); Hip dysplasia in 12 (32.4%) and complete dislocation in 4 infants (10.8%); Scoliosis in 14 (37.8%); Genu recurvatum was detected in 6 (16.2%) and patellar instability in 2 (5.4%). Genu valgum, Ankle instability, metatarsus adductus, kyphosis and fracture were diagnosed in one each (2.7%).
CONCLUSION: The prevalence of orthopaedic manifestations in children with PWS is similar to that of the adult literature. However, significant hip dysplasia and even complete dislocation requiring intervention was noted in a number of young infants. Hence we conclude that significant PWS related orthopaedic manifestations are common in childhood, and these should be actively assessed in early life and treated so as to allow children with PWS every chance to be active in older age.

4. NEW ASPECT OF PEDIATRIC DENTISTRY FOR CHILDREN WITH PRADER-WILLI SYNDROME IN JAPAN

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INTRODUCTION: There are few dentists interested in PWS in Japan, but dentistry is essential for the health of persons with PWS. The role of pediatric dentistry is not only to examine and treat dental diseases such as dental caries, but also to support children and their family's QOL from early childhood. Therefore it has a double mission, for children with PWS and also their families. From this aspect I will introduce a support network for children with PWS and their families in Kitakyushu city with this case presentation.
METHODS AND SUBJECT: 7 children with PWS, from 1 day to 6 months of age at the first visit. For the support network I, as a pediatric dentist, cooperate with pediatricians and peer counselors in Kitakyushu city.
RESULTS: To cope with dentistry problems I classified them into three categories. The 1st category is to support families as requested by pediatricians. The 2nd category is how to choose nursing methods for hypotonia and inactivity.
The 3rd category is to improve difficulty in weaning (or weaning failure), for example, too slow advance in weaning and/or persistently eating too soft weaning food. In the 1st category four cases were found, in the 2nd category one case and in the 3rd category two cases.
DISCUSSION: We started the support network for babies with congenital anomalies and their families in 1985 in Kitakyushu city. Since 2000 we have supported babies with PWS and their families. It is very important for the parents that an ongoing program of nursing and weaning is able to care for their child with care and nurturing. Most parents worry about their children becoming obese in the future and are prone to forget about the growth and the development of their children. In early infancy and childhood babies with PWS show severe hypotonia and have problems with nursing and weaning. Therefore systematic progress in nursing and feeding ability is very important. In this report, one case is under tube feeding at the age of 4, and in two cases weaning has advanced remarkably. Four children acquired good chewing ability and improved eating habits.

5. UNINARY INCONTINENCE IN PERSONS WITH PRADER-WILLI SYNDROME

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INTRODUCTION:Urinary incontinence (UI) is common in individuals with mental retardation in general, but has not been reported systematically in individuals with PWS so far. The aim of the study therefore was to assess and identify the frequency and type of UI, as well as associated symptoms in individuals with PWS.
METHODS:118 parents of individuals with PWS completed the Dutch version of the "Parental Questionnaire: Enuresis/Urinary Incontinence". This questionnaire includes items referring to day- and nighttime wetting, toilet habits, observable voiding behaviours and reactions, urinary tract infections, stool habits and behavioural symptoms.
RESULTS: The rate of nocturnal enuresis in persons with PWS was 13.6% at a mean age of 15.1 years. 3.8% had additional daytime urinary incontinence, and 3.3% had faecal incontinence. Lower urinary tract symptoms were common indicative of overactive bladder, dysfunctional voiding and postponement. Also, the rate of internalising and externalising behavioural problems was high.
CONCLUSIONS: Urinary incontinence is more common in persons PWS than in typically developing children, adolescents and adults. As lower urinary tract symptoms are common, detailed assessment and specific treatment of UI should be part of the care of all persons with PWS.

6. CORRELATION STUDY BETWEEN SCOLIOSIS AND GENETIC SUBTYPES IN CHILDREN WITH PRADER-WILLI SYNDROME (PWS)

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INTRODUCTION: Scoliosis was included as a supportive feature in the Consensus Diagnostic Criteria for PWS (Holm, 1993). A wide range of prevalence has been reported in different series of affected individuals. The aim of this study was to establish the prevalence of scoliosis in PWS affected children and its correlation with the different genetic subtypes.
PATIENTS AND METHODS: 83 children diagnosed by DNA methylation assay were included in this study. The genetic subtypes (deletion type I, deletion type II and mUPD) were established using MLPA technique and microsatellite analysis. Scoliosis was diagnosed by clinical and radiological studies. Cobb´s angle was used to determine the degree of scoliosis. The severity of scoliosis was established according to the age of onset and curve progression.
RESULTS: Mean age of the patients at follow-up was 11.04±6.64. Thirty-three (39.75%) children presented with scoliosis; the mean age at presentation was 6.42±4.9 years. Sixty four percent of patients with scoliosis have undergone brace treatment or surgery. For correlation purposes two of these patients were excluded since they had congenital hemivertebrae. Significant findings are shown in the Table below:

		Del I	Del II	mUPD	p (χ^2/Fisher)
Scoliosis	31/81	7/22	7/24	17/35	0.269
-Females	13/39	3/8	0/9	10/22	0.039
-Males	18/42	4/14	7/15	7/13	0.426
Severity					
-Mild	12	5	4	3	0.034
-Severe	19	2	3	14	

CONCLUSIONS: In this set of patients, the scoliosis prevalence was 39.75% being more frequent in the mUPD female group. The severity of scoliosis was higher in patients with mUPD.

7. DIFFERENT DISTRIBUTION OF GENETIC SUBTYPES OF PRADER-WILLI SYNDROME IN THE ELDERLY

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INTRODUCTION: Prader-Willi syndrome (PWS) is a genetic disorder caused by the absent expression of the paternal copy of maternally imprinted genes in chromosome region 15q11-13. The frequencies of different subtypes in PWS are usually given in the literature as 70% deletion, 25-30% mUPD and 3-5% others (IC defects and translocations). Little is known about factors that influence the frequency of genetic subtypes in PWS.
METHOD: The study sample comprised 102 adults with clinically and genetically confirmed PWS, contacted through the Dutch Prader-Willi Parent Association and physicians specialized in persons with Intellectual Disabilities (ID).
RESULTS: Genetic testing showed 55 persons (54%) with a paternal deletion, 44 persons (43%) with a mUPD and 3 persons (3%) with a defect of the imprinting center. This observed distribution differed statistically significant from literature (z-score: $p<0.05$). This result was mainly caused due to a higher proportion of mUPD in the advanced age groups. Differences in maternal age and BMI of the persons with PWS could not explain the differences in distribution across the age groups.
DISCUSSION: Our study population had a much broader age range, compared to other studies, because of a predominance of elderly people (40+) with PWS. In other studies these elderly persons might have been undiagnosed and/or underreported, due to a lack of genetic diagnosis. The results underline both the need for correct genetic diagnosis in all persons with PWS and adjustment of the guidelines for preventive management in adulthood.

8. CLINICAL FEATURES AND GENETICS OF VIETNAMESE PATIENTS WITH PRADER WILLI SYNDROME

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BACKGROUND: Prader-Willi syndrome (PWS) is a neurogenetic disease caused by abnormalities in genes located in 15q11q13 and characterized by neonatal hypotonia, retarded mental and motor development, hypogonadism, hyperphagia, morbid obesity and dysmorphic facial features. It has an incidence of 1:12.000-15.000 newborns. Seventy to seventy five percent of PWS cases are due to 15q11q13 deletions, 20-25% to uniparental disomy and 1% to mutations in the imprinting center.
AIM: We aim to describe the clinical, genetic and molecular features of patients with PWS, seen at the NHP, Hanoi, Vietnam.
PATIENTS AND METHODS: Descriptive study of 21 patients (13 males; 8 females) with PWS seen at the NHP, Hanoi, Vietnam during two years (2008-2009). Among 21 patients, 14 were confirmed diagnosis using fluorescence in situ hybridization (FISH) and 7 patients were confirmed diagnosis using DNA methylation analysis. Metaphase FISH was performed using SNRPN probe - red (15q11.2) and PML probe - green (15q24) for control. DNAs were extracted from lymphocytes of peripheral blood. Methylation test using DNA modified with sodium metabisulfite, followed by methylation-specific amplification using PCR of CpG island of SNRPN gene and analysis of the amplification products by electrophoresis on agarose gel.
RESULTS: Age at genetic diagnosis was 3.4 years (median = 1.9 years; range: 34 days-13 years). Twelve patients had a deletion confirmed by FISH, 2 patients had a deletion associated with translocation t(10;15),(6;15) confirmed by FISH. The methylation test revealed the sole presence of the maternally methylated allele in 7 patients. The clinical features included neonatal hypotonia (or history of hypotonia with poor suck) in all cases; global developmental delay (18/18); feeding problem in infancy (18/21); excessive weight gain (10/11); hyperphagia (10/12); hypogonadism (12/21); characteristic facial features (12/21); short stature (3/9) and diabetes mellitus type 2 associated with obesity in two cases.
CONCLUSIONS: Most Vietnamese patients with PWS have a deletion and the phenotype depends on age.

9. CLINICAL AND GENETIC ANALYSIS OF ELEVEN CASES WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Prader-Willi syndrome (PWS) is a multisystem disorder caused by absence of expression of the paternally active genes in the PWS critical region on 15q11-13. Clinical diagnostic criteria were established in 1993.We conducted a retrospective study of 11 patients suspected of having PWS using methylation-specific PCR(MS-PCR) assay to make the genetic diagnosis.
METHODS: The medical history of all 11 patients was reviewed. The major, minor and supportive features were recorded respectively according to the clinical diagnostic criteria. MS-PCR assay was applied for detecting genetic disorders in those patients.
RESULTS: All 11 patients were genetically diagnosed with PWS by MS-PCR analysis. Neonatal hypotonia with feeding problem, global developmental delay, hyperphagia-induced excessive weight again after 1 yr, and hypogonadism were the most frequently positive criteria. The mean total score of those 11 patients was 6.5 (8 required).
DISCUSSION: Consensus clinical diagnostic criteria are accurate, but the scores of the majority of our patients with PWS were less than the required 8 points. So the mainstay of diagnosis is DNA-based methylation testing to detect abnormal parent-specific imprinting. MS-PCR appears to be a specific, efficient and convenient assay, detecting more than 99% of affected individuals. It is important to confirm the diagnosis especially in those who have atypical findings or are too young to manifest sufficient features to make the diagnosis on clinical grounds. Age groupings based on characteristic phases of the natural history are suggested to serve to diagnose this syndrome in different stages of life.

10. STUDIES OF PRADER-WILLI SYNDROME PATIENTS IN TAIWAN IDENTIFY A NOVEL DELETION SPANNING THE PRADER-WILLI SYNDROME AND 15Q13.3 MICRODELETION SYNDROME CRITICAL REGIONS

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INTRODUCTION: In this study, we report clinical and molecular analyses of twenty-two Prader-Willi syndrome (PWS) patients from Taiwan.
METHODS: We conduct this study using methylation specific PCR, cytogenetic testing, microsatellite analysis and array CGH.
RESULTS: We identify 16 deletion patients (72.7 %), 5 uniparental disomy (UPD) patients (22.7 %) and one patient with imprinting defect (4.5%). Among the 16 deletion patients, we identify 6 type I deletion, 9 type II deletion and a type IV deletion. Of the 5 paternal UPD patients, we detect 4 maternal heterodisomic and one isodisomic case with homozygotic 15q.
DISCUSSION: In conclusion, our molecular analysis of 22 PWS patients from Taiwan suggests that there is no significant difference in etiology of PWS patients in Taiwan compared to that of Caucasian population. The phenotype of type IV patient did not depart significantly from the typical clinical picture of PWS, although some symptoms in the type IV patient were also reminiscent of the phenotype of individuals with the recently described 15q13.3 microdeletion syndrome.

11. PRADER WILLI SYNDROME PHENOTYPE IN A CHILEAN PATIENT WITH A 15Q11-Q13 TETRASOMY OF MATERNAL ORIGIN

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We present a female patient who was the product of the 6th pregnancy of young, healthy, nonconsanguineous parents following an uneventful pregnancy. Delivery was at term by C-section due to previous C-sections, and there was no relevant family history. Her development was delayed: she sat at 12 months, pulled to stand at 19 months, and she has no walking and no language at 19 months. Early in her life she was referred to neurological evaluation because of concerns regarding hypotonia, abnormal hearing and development delay. She does not present any behavioral problems and she started early intervention at 3 months. General exams, including brain MRI, metabolic studies, hearing, ophthalmologic and neuromuscular evaluations, were normal. In the Genetics evaluation performed at 19 months of age, the patient was found to have: height 80 cm (30%), weight 10.650 K (25%), head circumference 47 cm (50%); head symmetry with narrow bifrontal diameter, almond shaped palpebral fissures, ears normally placed and shaped, normal nose; small hands and feet; normal female genitalia, Tanner I. Hypotonia, increased laxity and developmental delay were also noted. With these clinical findings, Prader Willi syndrome was suspected. Methylation testing was normal and her chromosome analysis revealed 46, XX, dup (15) (q11.2-q13), that was confirmed by FISH analysis. Parental karyotypes were normal. By MLPA analysis it was found that the patient has a twofold increased dosage for all probes representing the Prader-Willi/Angelman syndrome (PWS/AS) region, indicating that she was tetrasomic for this region. Another methylation analysis revealed that the additional copies were of maternal origin.

Since dosage for the *APBA2* gene, which maps telomeric to the PWS/AS region, was also increased, MLPA analysis was performed with the MLPA kit P343-B1 Autism-1 to find out the extent of the triplication. Interestingly, there was a twofold increased dosage for two additional loci, *NDNL2* and *TJP1*, and a 1.5 fold increased dosage for *MTMR15*, *TRPM1*, *KLF13* and *CHRNA7*. For the *SCG5* gene the patient showed a normal dosage. These findings indicate that the patient has one additional copy from breakpoint cluster region BP1-BP5 and one additional copy for the region BP1-BP4.

At her last evaluation at 2 years 2 months of age, she had improved in her language during the previous five months.

To our knowledge, this is the first case described with this abnormality and suggests that patients with hypotonia and features of PWS may be susceptible to this alteration.

12. DIAGNOSIS OF PRADER-WILLI SYNDROME BY METHYLATION-SPECIFIC PCR METHOD IN CHINESE MAINLAND

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INTRODUCTION: Methylation-Specific PCR(MS-PCR) assay for the diagnosis of Prader-WillisSyndrome (PWS) has been widely applied overseas for years, but it hasn't been clinically used for PWS diagnosis in Chinese mainland. The purpose of this article was to establish MS-PCR assay for the diagnosis of PWS and facilitate its applications clinically in Chinese mainland.
METHODS: Sixty eight participants were divided into three groups: normal controls (16), typical PWS patients (7) and suspected patients (45). Genome DNA was extracted by salt fractionation method and treated with CpGemone™ Fast Modification Kit. Using unmodified genome DNA as a system control, the modified DNA was amplified by PCR with two primer pairs (Maternal and Paternal), and was separated by agarose gel electrophoresis.
RESULTS: 1) All normal controls showed both 174bp (Maternal) and 100bp (Paternal) products, while all seven typical PWS patients, consistent with the clinical diagnosis, demonstrated only 174bp (M) product. 2) In the 45 suspected patients, 11 cases were confirmed to be PWS by MS-PCR, while the others were excluded from PWS.
CONCLUSIONS: Eighteen PWS patients have been diagnosed by MS-PCR. The MS-PCR was established as a specific, efficient and convenient method to diagnose PWS in Chinese mainland. Based on this, we can do more practice for further clinical evaluation, treatment, and scientific research in Chinese mainland.

13. SINGLE TUBE AND HIGH THROUGHPUT GENOTYPING OF PRADER-WILLI AND ANGELMAN SYNDROMES BY REAL-TIME PCR WITH METHYLATION-SENSITIVE HIGH-RESOLUTION MELTING ANALYSIS

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INTRODUCTION: Most of Prader-Willi syndrome (PWS) and Angelman syndrome (AS) resulted from deletion at a common region of chromosomal 15q11-13 or uniparental disomy (UPD) of chromosome 15. Validation of diagnostic assays are challenging because most of tools can not distinguish deletion type from UPD type.
METHODS: We introduce a novel, in-house designed real-time PCR with methylation-sensitive melting analysis (MS-HRM) method for a rapid diagnosis of PWS and AS associated with deletion or UPD in a single tube. The SYBR green-based real-time PCR is used for determination of copy number and the extended MS-HRM analysis is for identification methylation status of the *SNRPN* gene. We established this single tube assay for the analysis of 38 individuals with Prader-Willi syndrome, 2 individuals with Angelman syndrome, and 28 unaffected individuals.
RESULTS: In the PWS patients, the mutation type was uniparental disomy (UPD) in thirteen of them and deletion type in the rest of them. One of the two samplesfrom individuals with clinical suspicion of AS was molecular diagnosed as UPD while the other one had one maternal allele and one paternal allele. The genotyping results obtained were fully concordant with traditional methylation PCR.
CONCLUSIONS: Our results show that the real-time PCR with MS-HRM strategy is a good alternative for molecular diagnosis of PWS and AS. The in-house protocol provides detailed information about deletion and UPD genotypes as a significant strategy in clinical application for epigenetics in a routine laboratory.

14. DIFFERENCES IN GH-RELATED PARAMETERS AND GH RESPONSES BETWEEN PATIENTS WITH PRADER-WILLI SYNDROME DUE TO DELETION AND MATERNAL UNIPARENTAL DISOMY 15

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INTRODUCTION: Short stature and decreased growth rate are common features in children with Prader-Willi syndrome (PWS). Many patients have a decreased GH secretion, low IGF-I levels, and a positive response to GH treatment. Grugni et al. (2008) has reported that GHRH + arginine induced GH secretion in adult PWS patients with deletion is significantly higher than those with maternal uniparental disomy 15 (upd(15)mat). However, there was no report comparing GH-related parameters and GH responses between patients with deletions and those with upd(15)mat in terms of provocative tests. Here, we studied Japanese prepubertal PWS patients treated with GH.
METHODS: Seventy-six prepubertal PWS patients treated with GH (M:F = 47:29, deletion: upd(15)mat 55:21, age at start of GH: median 3.5, range 0-13) were included in this study. We measured height, weight, IGF-I, IGFBP3 and GH responses to agrinine or insulin stimulation test just prior to start of GH. Height, weight, serum IGF-I, and serum IGFBP3 were annually obtained in one center after start of GH therapy. SD scores of height were calculated according to PWS reference values of Japanese (SDS_{PWS}). We compared these data between patients with PWS due to deletion (deletion group) and upd(15)mat (disomy group).
RESULTS: Age and body mass index at start of GH were similar between the two groups (median 3.5years, range 0-13.5 vs. 3.6years, range 0-11, p=0.92; BMI 17.2±4.7 vs. 17.3±3.0, p=0.97), while the GH response to insulin stimulation was significantly lower in the disomy group than in the deletion group (GH peak 3.60±2.2 ng/ml vs. 11.1±8.6 ng/ml, p=0.0013). There were no significant differences in GH response to arginine (p=0.092), height SDS_{PWS} at start of GH (p=0.46), IGF-I (p=0.30), IGFBP3 (p=0.56), and gain of SDS_{PWS} (1yr after: p=0.14, 2yrs after: p=0.56).
DISCUSSION: These findings suggest that GH response to insulin is significantly different in PWS individuals who have separate genetic subtypes even in the prepubertal age. The lower response of GH secretion in UPD type suggests better responsiveness to GH treatment in UPD than in deletion type, but no significant differences were observed between the two groups.

15. GH SECRETION AMONG ADULT PATIENTS WITH PRADER-WILLI SYNDROME DUE TO DIFFERENT GENETIC SUBTYPES

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INTRODUCTION: The clinical phenotype of Prader-Willi syndrome (PWS) can be variably related to the underlying genetic abnormality. PWS patients with maternal uniparental disomy of the chromosome 15 (UPD15) have fewer facial features, less hypopigmentation and higher levels of psychosis compared to subjects with deletion in the paternally-derived chromosome 15 (del15q11-q13). PWS individuals carrying the larger type I (TI) deletion suffer from greater behavioural problems than patients with the smaller type II (TII) deletion. However, these findings are not considered to be unequivocal and the clinical impact of genetic subtype appears to be extremely complex. Few data are currently available on the relationship existing between endocrine abnormalities in PWS subjects and the different genetic subtypes. The aim of this study was to investigate the GH response to combined GHRH+arginine administration in PWS patients with different types of deletion and those with UPD15.
METHODS: Thirty-seven patients, 14 males, aged 17.5-41.2 yr, with PWS due to TI deletion (n. 6), TII deletion (n. 15) or UPD15 (n. 16), were studied. Pituitary GH secretion was evaluated by dynamic testing with GHRH+arginine.
RESULTS: Both the mean peak GH response and the integrated GH secretion (GH AUC and GH nAUC) for the UPD15 patients (4.6±1.6 µg/l, 241.6±71.7 µg/l/h and 228.3±71.6 µg/l/h, respectively) were lower than that observed in all subjects with del15q11-q13 (9.1±1.8 µg/l, 547.0±132.3 µg/l/h and 514.9±127.6 µg/l/h: $p<0.005$), as well as in TI (7.7±1.2 µg/l: $p<0.02$; 424.2±88.8 µg/l/h and 393.4±88.8 µg/l/h: $p<0.05$) and TII (9.6±2.6µg/l, 587.9±174.2 µg/l/h and 555.4±167.6 µg/l/h: $p<0.01$) deletion groups. TI and TII groups had similar stimulated GH levels and integrated GH secretion. 43.5% of our PWS had severe GHD. However, the percentage of GHD was higher in UPD15 subjects (62.5%) than in individuals with del15q11-q13 (28.5%).
DISCUSSION: Our results are in agreement with the hypothesis that a derangement of GH/IGF-I axis occurred in PWS, indicating that GHD is a common feature of adult patients with PWS. Specifically, our data point to differentiating the pattern of GH secretion by genetic subtypes, with higher GH responses in typical deletion subjects when compared to patients with UPD15. In this view, our data underscore the need to test PWS adults for diagnosis of GHD, particularly in subjects with UPD15. Finally, our results did not show significant differences in GH secretion among TI and TII PWS deletion patients. These data are similar to what has been observed in prior studies on cognitive and behavioural features. However, further investigation of larger number of individuals seems to be required to determine whether there are any true phenotypic differences between the two classes of deletion.

16. GROWTH HORMONE THERAPY IMPROVES HYPERLIPIDEMIA IN CHILDREN WITH PRADER-WILLI SYNDROME.

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INTRODUCTION: Hyperlipidemia in children with Prader-Willi syndrome (PWS) is generally mild. Increased adipose tissue mass, high caloric intake, growth hormone (GH) deficiency, and diabetes mellitus (DM) have been considered as factors affecting lipid metabolism in PWS. GH therapy has favorable effects on lipid metabolism by increasing LDL receptor, decreasing adipose tissue and so forth. On the other hand, unfavorable effects such as increasing insulin resistance have also been reported. We examined the influence of GH on lipid metabolism of PWS patients.
METHODS: Medical records of 53 patients (33 boys, 20 girls) on GH were examined retrospectively. Median age at the commencement of GH was 3.5 years (0.7-14.1). Serum lipid parameters (Tcho, TG, LDL, HDL), HbA1C, HOMA-R, and body composition by DEXA (%FAT) were examined at 0, 6, and 12 months after the commencement of GH therapy. The most recent data (median 4.6 years; 1.0-9.6 years) were also obtained.
RESULTS: Lipid profile before GH was normal (median: Tcho 192.0, TG 78.0, LDL 117.0, HDL 52.0 mg/dl). The lipid parameters did not show significant changes between before and after GH therapy at any time points, though a tendency of decreasing Tcho (commencement →latest:192→184mg/dl), decreasing LDL (117→107mg/dl), and increasing HDL(52→60 mg/dl) were seen. %FAT significantly decreased ($p<0.0001$) with GH therapy. %FAT change did not show any relationshipto lipid parameter changes. Insulin resistance (HOMA-R) increased significantly (median: 0.9→1.8) during GH therapy but HbA1C did not show a significant change. Two patients were started on GH with high HbA1c level (>6.5%). Their HbA1c decreased to normal after the therapy. One patient on GH developed DM after 7 years of therapy. Hyperlipidemia (Tcho> 210mg/dl) was seen in 15 patients before GH. The lipid profile of the hyperlipidemia group showed high Tcho & LDL, and low HDL. In the hyperlipidemia group, Tcho decreased significantly (224→204 mg/dl; $P<0.05$) with GH therapy. LDL also tended to decrease (162→126 mg/dl) and HDL increased (47→56 mg/dl). TG did not change. There were no significant relationships between the changes in %FAT and the changes in lipid parameters during the therapy in the hyperlipidemia group.
DISCUSSION: GH therapy tended to decrease Tcho, LDL and to increase HDL especially for the hyperlipidemia group. These favorable effects on lipid metabolism were not induced by improvement of body composition. Other mechanisms of GH treatment such as increasing LDL receptor might play a role in these favorable effects. GH therapy in PWS is a safe and effective treatment with regard to lipid metabolism.

17. THE MEASUREMENT OF PARAVERTEBRAL MSUCLE VOLUME CAN BE A USEFUL INDICATOR OF PROGRESSION OF SCOLIOSIS IN PWS WITH GH THERAPY

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INTRODUCTION: Poor muscle strength in paravertebral muscle is considered to be one of the exacerbating factors of scoliosis in PWS. In addition, there is a concern that growth hormone (GH) therapy, which has been started worldwide, can be an unfavorable factor on scoliosis. The purpose of this study was, firstly, to investigate the clinical course of scoliosis in PWS patients with GH therapy and secondly, to examine whether paravartebral muscle volume can be a candidate indicator of the progression of scoliosis in these patients.
SUBJECTS & METHODS: Thirty five patients with PWS on GH treatment (22 males and 13 females, ages ranging from 2 to 16 y/o, deletion type in 24 and UPD type in 11 patients) were evaluated. Observation period ranged from 6 to 41 months. To evaluate the degree of scoliosis, Cobb angles were measured every 6 months during GH therapy. Simultaneously, one slice of CT scan was obtained at the level of umbilicus to evaluate paravertebral muscle volume. Cross-sectional areas of paravertebral muscles were measured. The rate of increase of total bilateral paravertebral muscle volume (%/year) was defined as [{latest total muscle volume−first total muscle volume} x 100]/ {first total muscle volume x period of observation (year)}. The difference of paravertebral muscle volume of right and left side (%) was defined as {(larger muscle volume−smaller muscle volume) x 100} / smaller muscle volume.
RESULTS: Twenty two patients never developed scoliosis (no scoliosis group). Scoliosis did not progress in 5 (unchanged group), progressed in 6 (progressed group) and improved in 2 patients (improved group). The mean rates of increase of paravertebral muscle volume in each of these four groups were 41.8, 32.4, 11.7 and 43.3%/year, respectively. The mean differences of paravertebral muscle volume of right and left side in the initial CT scan were 8.4, 9.8, 10.0 and 3.0%, respectively. The mean differences of paravertebral muscle volume of right and left side in the latest CT scan were 4.1, 4.5, 12.5 and 4.1%, respectively.
DISCUSSION: The clinical courses of scoliosis in PWS patients with GH therapy were variable. Although in many patients scoliosis was exacerbated, improvement was seen in some patients. Paravertebral muscle volume increased more in patients with favorable outcome (no scoliosis, unchanged and improved group) than in those with progressed scoliosis (progressed group). Similarly, the degree of asymmetry of paravertebral muscle diminished more in patients with favorable outcome than in those with progressed scoliosis.
CONCLUSION: Poor increase of paravertebral muscle volume and/or poor improvement in its asymmetry could be useful indicators for progression of scoliosis in PWS with GH therapy.

18. THE GH/IGF-I AXIS AND PITUITARY FUNCTION AND SIZE IN ADULTS WITH PRADER-WILLI SYNDROME

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CONTEXT: In adults with PWS, limited information is available about pituitary function, more specifically the prevalence of growth hormone deficiency.

OBJECTIVE: To gain more insight into endocrine function, with emphasis on growth hormone secretion, in PWS adults.

DESIGN: Measurements of basal pituitary hormone levels and a combined GHRH-Arginine test were performed. Size of the pituitary gland was measured on MRI images.

SETTING: The study was conducted in the clinical research unit of the VU University Medical Center.

PATIENTS: Fifteen randomly selected adult PWS individuals were included and 14 healthy brothers and sisters served as a control group.

MAIN OUTCOME MEASURES: IGF-I and IGFBP-3 levels and peak GH level after a combined GHRH-Arginine test were measured. GHD was defined by standard criteria for GHD and BMI-related cut off points. Other pituitary hormone deficits are diagnosed based on serum levels of the hormones concerned.

RESULTS: In adult PWS subjects, IGF-I levels were low when compared to healthy controls and IGFBP-3 levels were normal. GHD was diagnosed in 23-38 % of the PWS patients depending on the criteria being used. Peak GH level was strongly correlated with weight, BMI, waist and fat mass. Hypogonadism was present in 87 % of the patients. Hypothyroidism and adrenal insufficiency could also be demonstrated. Anterior pituitary size was lower in PWS individuals when compared to healthy controls.

CONCLUSIONS: GHD and other pituitary hormone deficits are demonstrated in a considerable percentage of adult PWS patients. Early detection and treatment of pituitary hormone deficits in adult PWS individuals can have major therapeutic consequences.

19. LONG-TERM GH THERAPY AND GLUCOSE METABOLISM IN ADULTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: GH deficiency may be present in a significant percentage of adult patients with Prader-Willi syndrome (PWS). These findings seem to be strengthened by the beneficial effects of replacement therapy with GH (GHT) in these individuals. However, doubt on whether GHT can impair glucose homeostasis in subjects prone to develop diabetes have risen in the last years. In fact, type 2 diabetes mellitus (DM2) frequently appears during or soon after puberty as a complication in 7-20% of patients with PWS. Altered glucose metabolism occurs despite the evidence that PWS individuals are more insulin sensitive than subjects with simple obesity. To date, few data have been reported on changes induced by prolonged GHT on glucose and insulin homeostasis in PWS during adulthood (Hoybye, 2007). The objective of our study is to further investigate the impact of long-term GHT on the carbohydrate metabolism in a group of adult subjects affected by PWS.
METHODS: Six PWS patients, 5 males, aged 21.1-29.1 years, participated in the study. Five subjects had del15q11-q13 and UPD15 was found in the remaining female. After baseline evaluation, patients received GHT at a mean starting dose of 0.021±0.001 mg/kg/wk for the first month. Subsequently the GH dose was adjusted to reach the 50th percentile of normal serum IGF-I for sex and age. Both in basal condition and after 24, 48 and 72 months, a standard oral glucose tolerance test (OGTT) was carried out. Physical examination included measurements of weight, height and Body Mass Index (BMI). No subject was treated with drugs which could affect carbohydrate or insulin metabolism. Both the quantitative insulin-sensitivity check index (QUICKI) and the homeostasis model assessment of insulin resistance (HOMA-IR) were calculated. Hyperinsulinaemia was defined when fasting insulin levels were greater than 26 mU/l, or insulin peak levels (during OGTT) >150 U/ml and/or >75 mU/l at 120 min of OGTT. Impaired glucose tolerance (IGT) and DM2 were defined on the basis of the American Diabetes Association criteria (Diabetes Care 2005).
RESULTS: Clinical and laboratory data of PWS patients during GHT are summarised in the Table; for significance: *p<0.005 *vs* basal; **p<0.05 *vs* basal.

	basal	2 yr	4 yr	6 yr
BMI	45.2±1.6	45.1±2.7	42.3±1.5	42.1±2.3
IGF-I ng/ml	88±16	223±36*	229±35*	314±46*
HbA1c%	5.6±0.1	5.3±0.2	5.3±0.1*	5.3±0.1*
Hyperinsulinism	3	2	2	2
IGT	0	0	0	2
DM2	0	0	0	0
QUICKI	0.375±0.02	0.360±0.02**	0.358±0.02	0.369±0.02
HOMA-IR	1.52±0.37	1.86±0.45**	2.22±0.63	1.94±0.60

DISCUSSION: Altogether, our findings seem to demonstrate that carbohydrate metabolism is not impaired by GHT in the majority of PWS adults. However, the occurrence of IGT during GHT in 2 PWS with rapid weight gain suggests that close surveillance of glucose and insulin homeostasis and low doses of GH should be applied, especially if the PWS patient is very obese.

20. DIABETES MELLITUS IN PRADER-WILLI SYNDROME ---FREQUENCY, RISK FACTORS, AND THERAPY

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INTRODUCTION: The frequency of diabetes mellitus (DM) in Prader-Willi syndrome (PWS) in adults has been reported to be around 20%, but no Japanese data exist. Several factors, including overweight and massive visceral adiposity, have been considered as risk factors for DM. Because of mental subnormality and uncontrollable appetite, insulin therapy has been controversial in PWS.
SUBJECTS & METHODS: Sixty-five patients, aged from 10 to 53 years, were studied retrospectively. Risk factors (age, sex, genotypes, gestational age, birth weight, BMI, familial tendency to DM, and growth hormone (GH) use) were analyzed.
RESULTS: The frequency of DM over 10 years of age was 26.2% (17/65 patients). The frequency of DM was high at the ages of 10-15 years and 28-30 years. There were no significant differences between DM and non-DM groups by sex, genotype, or GH use. Age and BMI showed significant differences between these 2 groups ($P<0.05$ and $P<0.01$, respectively). Three of 17 patients (17.6%) with DM had a family history of DM. Insulin resistance (HOMA-R >2.5) was seen in 7 of 10 patients who was tested and low insulin secretion (urine C-peptide <20μg/day) was seen in 2 of 6 tested patients. Proteinuria in 1 patient (5.9%), micro-albuminuria in 4 (23.5%), and simple retinopathy in 2 (11.8%) were observed. Eleven out of 17 patients (64.7%) were treated with insulin and insulin was successfully discontinued in 3 patients.
DISCUSSION: The frequency of DM in PWS in Japan was 26.2%, which was compatible with the reported frequency. The most common age of onset of DM was 10-15 years, which was younger than previously described. Obesity was a risk factor of DM, and insulin-resistant DM was more common than poor insulin-secretion DM. Insulin therapy was used for as much as 65% of our patients and was safe and successful

21. CLINICAL MANIFESTATIONS AND ENDOCRINE CHARACTERISTICS IN PATIENTS WITH PRADER-WILLI SYNDROME

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OBJECTIVES: Prader-Willi syndrome (PWS) is a complex, multisystem disorder, caused by absence of expression of the paternally active genes in the PWS critical region on chromosome 15q11-13. Our purpose is to evaluate the endocrine situation for the patients primarily in China.
METHODS: Physical examination, laboratory examination and endocrine examination were obtained in 11 patients (including 5 males and 6 females, aged 10.5±5.2 years) whose diagnosis was confirmed by the MSPCR method.
RESULTS: The results of primary evaluation for the 11 patients were as following: (1) physical examination and laboratory examination: obesity in all the patients; short stature in 3 patients who were pre-school age; normal or higher than normal stature in 5 patients who were school age; but short stature in all the patients who were older than 15 years. Biochemical Index was mildly abnormal in all the patients. The level of hs-CRP was increased in all the patients. (2) endocrine examination: The growth hormone stimulation test was performed in 7 patients, and all the results showed growth hormone deficiency. In the patient older than 16 years, the serum level of testosterone in this male patient was decreased, and the serum level of E2, FSH and LH were decreased. The incidence of the diabetes was 44.5%, but there was no difference between the patients with diabetes and the patients without diabetes in age or BMI; the homeostasis model assessment–insulin resistance (HOMA-IR) was tested in 6 patients (2.2±2.0), but there was no difference detected among the patients between healthy children and simple obesity ($P>0.05$).
CONCLUSIONS: Our study accumulated clinical experience for Chinese patients in PWS, especially in abnormalities of the endocrine system. But the limitation of the study is that the size of the sample is not large enough to expound the real condition of endocrine characteristics in patients. We will collect more samples for further study. And the epigenetics research and the treatment will be our next step for this series of studies.

22. BODY COMPOSITION ASSESSMENT WITH BIOELECTRICAL IMPEDANCE ANALYSIS IN PATIENTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Knowledge of body composition assessment in patients with Prader-Willi syndrome (PWS) is of importance. We report our experience of assessing body composition by using eight-polar bioelectrical impedance analysis (BIA) for PWS in Taiwan.
METHODS: Multi-frequency BIA with eight tactile electrodes (InBody 3.0, Biospace, Seoul, Korea) were performed in 30 patients with PWS (16 males and 14 females; mean age, 8.1 ± 3.8 years; age range, 3 years to 19 years). None had received growth hormone treatment at the time of this study.
RESULTS: Twenty-five patients with PWS were diagnosed with deletion type, and 5 with uniparental disomy. The standard deviation scores (SDS) of height, weight and body mass index (BMI) were -0.97±1.29, 2.28±2.66 and 3.14±2.74, respectively. The percentages of total body water, body fat, and soft lean mass were 36.6 ± 7.3%, 45.9 ± 10.8%, and 49.9 ± 9.9%, respectively. The fat distribution with waist-hip ratio (WHR) was 1.01 ± 0.13. The body fat percentage was positively associated with weight SDS ($r = 0.581$, $p < 0.01$), BMI SDS ($r = 0.665$, $p < 0.01$) and fat distribution with WHR ($r = 0.431$, $p < 0.05$), and negatively associated with total body water percentage ($r = -0.997$, $p < 0.001$) and soft lean mass percentage ($r = -0.996$, $p < 0.001$). There were no significant associations between gender or genotype pattern (deletion vs. uniparental disomy) and the results of BIA.
CONCLUSIONS: The present study showed significantly higher body fat and lower total body water percentages among patients with PWS compared with normal children. Lower height, heavier weight, higher BMI, and higher WHR among these patients were also observed. These findings and the follow-up data will help with the quality of care for PWS patients. Multi-frequency BIA is a rapid, painless, and noninvasive method for evaluating the body composition of patients with PWS.

23. PWS HYPERPHAGIA IS NOT DUE TO IMPAIRED GLP-1 OR PYY SECRETION

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INTRODUCTION: Prader-Willi syndrome (PWS) is a leading genetic cause of obesity, characterised by hyperphagia, endocrine and behavioural disorders. It has been suggested that the intense hyperphagia in PWS could, in part, stem from impaired satiety signalling by gut hormones after meal ingestion. Key hormones with a physiological role in satiety include GLP-1 and PYY, released from the intestinal L-cells. A major confounding factor in previous studies investigating these hormones has been the difference in body composition in PWS subjects being compared with other obese subjects, as differences in adiposity may affect circulating hormone levels.
METHODS: 9 subjects with PWS, 12 matched healthy obese subjects and 10 healthy normal weight subjects were offered a standardised breakfast (600 kCal). GLP-1(Active), PYY(Total), PYY(3-36) and Ghrelin(Total) were measured by ELISA or radioimmunoassay at baseline and for 4 hr postprandially. Body composition was assessed by Dual X-ray Absorptiometry. A visual analogue scale was used hourly to assess appetite and fullness.
RESULTS: PWS and Obese groups were matched for BMI, percentage body fat and central abdominal fat mass. The PWS group had a significantly higher postprandial secretion of PYY (Total) ($p=0.02$) and a trend towards higher GLP-1 secretion ($p=0.08$) compared to the obese group. Fasting Ghrelin levels were elevated in PWS, and dropped by 20% postprandially, whereas low Ghrelin levels in obese subjects did not change. There was no significant difference in self-reported fullness between groups, however, the PWS group reported a lack of appetite suppression postprandially.
CONCLUSIONS: When compared to adiposity matched control subjects, hyperphagia in PWS is not related to impairment in postprandial GLP-1 or PYY secretion, or abnormal postprandial Ghrelin suppression. Indeed, higher levels of GLP-1 and PYY without an associated increase in feelings of fullness suggest that any impairment in this system may lie at, or beyond, the level of GLP-1 and NPY receptors in the brain, and not at the level of the intestinal L-cells, as it is suggested for non-syndromic obesity.

24. WEIGHT CONTROL IN PRADER-WILLI SYNDROME PATIENTS ACHIEVED BY DISEASE SPECIFIC REHABILITATION

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INTRODUCTION: Our study represents an attempt to respond to what we felt was an insufficiently heard social need: weight control in the late teen-ager and adult PWS population. For this reason we set up a rehabilitation approach based on periodic residential rehabilitation cycles specifically customized to Prader-Willi syndrome patients (PWRs).
To review the efficacy of a multidisciplinary rehabilitation approach for weight control in adult patients affected by Prader-Willi syndrome (PWS), we analyzed retrospectively data obtained during the period 2002-2008.
METHODS: We analyzed 53 PWS subjects suffering from severe obesity. A multidisciplinary approach was used to reduce obesity in adult PWS patients. A 1500 Kcal daily diet is associated with intense physical exercise during 4 week cycles organized 4 times a year. Endurance to physical training was achieved by music therapy, psychomotricity, educational and entertainment activities.
RESULTS: BMI decreased on average by 2.1 points (standard error of the mean, SEM 0.16) per training when PWS subjects attended the rehabilitation treatment for 4 weeks. In 3 patients who attended our treatments regularly, we recorded a BMI reduction of 8.9 (SEM 4.2) over 6 years. We observed a statistically significant gender difference in weight loss during the treatment and a trend in weight gain after discharge. Males lost weight 1.5 fold more than females. Similarly, even if both genders maintained substantially the weight loss for the first 6 months after dismissal, afterwards males tended to gain weight faster than females.
CONCLUSIONS: Our data show successful weight control in adult PWS patients based on intense and prolonged physical exercise with normal daily calorie intake. The application of the proposed adjuvant approach could be suited also to other obesity syndromes with mental retardation.

25. EXERCISE ON HAND – THE BENEFITS OF IN-HOME EXERCISE EQUIPMENT FOR PATIENTS WITH PRADER-WILLI SYNDROME

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INTRODUCTION: In a multi-disciplinary public hospital PWS clinic, exercise is prescribed, in principle, as a "mandatory" part of the patient's ongoing health care program. The clinical impression is that patients who have exercise equipment within their homes improve their weight and health profile more than those who exercise outside the home. People with PWS like sameness but adapt well to consistency and regularity of new procedures. Most PWS patients require extensive external motivation to exercise and all require their caloric intake to be managed by others. Residential environments are likely to determine the success of their progress.

METHODS: Twenty six PWS patients were studied retrospectively to determine the efficacy of having exercise equipment within their residence. Four groups of clients were defined according to the availability and non availability of in-home exercise equipment for a period of at least 12 months. The weight loss of patients with in-home exercise equipment (WIHE) was compared with those with no in-home exercise equipment (NIHE). Comparisons were also made between weight lost during 2 different 12 month periods for the same patients - when they had no in-home equipment (SNIHE) and when they did have in-home equipment (SWIHE). All clients in all groups reported participating in some form of exercise during the 12 month period studied. Data was only included in analysis if there were no major outside influences that may have been affecting weight loss e.g. major hospitalisation, change of residence etc. All clients were reported to be living within residences where restrictive food practices were in place. The majority of clients in all groups lived in a supported group-home environment where exercise and consistency in management were deemed duty of care. All clients were prescribed and encouraged to perform effective exercise for 15-40 minutes 5-6 times per week.

RESULTS: There were no significant differences between the groups at baseline for any of the demographic or anthropometric measurements collected. The weight loss for the WIHE group (9.8 $\pm$ 5.9 kg) compared to the NIHE group (mean=-2.1 $\pm$ 4.2 kg) after a12 month period was highly significantly different ($p<0.0001$). There was also a significant difference in weight loss between SWIHE and SNIHE groups ($p<0.0001$) over a 12 month period.

DISCUSSION: Exercise is well recognised to be important in managing chronic illness and general health. It is also used extensively to help manage weight in the obese subject. This study has demonstrated that for PWS clients with exercise equipment in the home exercise recommendations were more likely to be met and significantly more weight loss was achieved than those without in house exercise equipment.

CONCLUSION: The provision of in-home exercise equipment may be imperative for meeting exercise prescription and weight management goals of people with PWS.

26. BARIATRIC SURGERY IN PRADER-WILLI SYNDROME: LONG-TERM FOLLOW-UP AFTER BILIOPANCREATIC DIVERSION

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INTRODUCTION: The benefits of bariatric surgery in obese patients are well known, but data are lacking regarding the long-term outcome of the surgery in Prader-Willi syndrome (PWS). Excessive weight gain is identified as the main cause of morbidity and mortality in PWS individuals. Dietary restriction and anorexic drugs are generally ineffective to induce a permanent weight loss. Thus, surgical treatment of morbid obesity in PWS remains a realistic solution.

METHODS: We report six patients with genetically confirmed PWS, associated with morbid obesity, who underwent Scopinaro's biliopancreatic diversion (BPD) (table). No perioperative complications were observed. All patients systematically received iron, calcium, vitamin D, minerals, and mulvitamin preparations to prevent any potential nutritional deficiency.

			after	BPD	before	BPD	maximum
pts	sex	karyotype	age (yr)	BMI	months	BMI	weight loss
1	F	UPD	15	56.6	149	63.5	24.5
2	M	del15	16	31.7	240	42.8	7.0
3	M	del15	16	53.8	123	52.9	47.5
4	F	UPD	18	51.5	100	55.9	30.0
5	M	del15	19	48.6	198	38.8	25.5
6	F	del15	20	49.0	60	45.1	20.1
mean±SE			17.3±0.8	48.5±3.6	145±26.8	49.8±3.7	25.8±5.4

RESULTS: Anthropometric data after BPD are reported in Table. All subjects had hypochromic anemia. Five individuals showed a severe reduction of bone mass density by DEXA, while 4 patients had obstructive sleep apnoea during polysomnography study. No effect of BPD on hyperphagia was observed.

DISCUSSION: Our findings show a significant weight loss in 2 patients after bariatric surgery, whereas the absence of weight loss or the regain of weight in four subjects suggests that even BPD may be ineffective for long-term control of obesity in PWS. Because all 3 components of BPD (the gastric remnant, the length of the alimentary channel, and the length of the common channel) influence weight loss, it is possible that our negative results may be related to the large gastric remnant (250 mL). In this regard, it has been reported that BPD with duodenal switch and smaller gastric remnant (100 mL) offers good results without the need for revision (Papavramidis et al, J Pediatr Surg 2006). However, bariatric procedures have generally demonstrated poor results in PWS patients in comparison with normal obese individuals. PWS subjects are such aggressive eaters that the need for dietary intervention and monitoring is not eliminated after malabsorptive operation. In conclusion, the optimal therapeutic procedure for PWS seems to be far from settled. In this context, bariatric surgery should be taken into consideration only in selected cases in which severe obesity-related morbidities are present and rapid weight loss is considered to be potentially beneficial.

27. VAGUS NERVE STIMULATION IN CURBING HYPERPHAGIA IN PRADER-WILLI SYNDROME

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INTRODUCTION: Prader-Willi syndrome (PWS) is associated with hyperphagia that results from decreased satiety signalling. The vagus nerve is centrally involved in satiety signalling and may be implicated in PWS. Vagus Nerve Stimulation Therapy® (VNS; Cyberonics, TX, USA) is licensed for drug-resistant epilepsy and depression. As a by-product, some people receiving VNS therapy have reported weight loss (Pardo et al, 2007), and VNS-altered food craving has been demonstrated empirically (Bodelenos 2007). We are assessing the safety, acceptability and efficacy of VNS as a novel treatment for hyperphagia in PWS.
METHODS: Two individuals with PWS (1 male, 1 female), recruited through the PWS Association-UK, have been surgically implanted with VNS with a third participant scheduled. Implantation of VNS took place after assessments for suitability. Following implantation there was a three month period during which the VNS was implanted but switched off. After three months, the VNS was set to 30Hz with an output current of 0.25mA and a signal on time of 30secs, and off time of five minutes. To date, one participant has had VNS switched on. Since implantation, participants have attended monthly visits to assess VNS. Outcome measures: Safety: sleep apnoea incidents, ECG measurements, consultation on side-effects. Acceptability: participants self-report and diaries of side-effects. Efficacy: weight, body composition, hormone levels, fMRI responses to food images, body image, carers' reports, and automated measures of eating rate and quantity.
RESULTS: Safety: VNS has so far had no effect on sleep apnoea incidents and has not shown adverse effects on heart rate as tested at implantation and at switch-on in our first participant. When switched off, VNS has been proven safe to use in 3T MRI scanning at least six weeks post-implantation and using a USA Instruments TxRx coil only. Acceptability: At the current settings, VNS has not led to any side effects which have caused concern to the participant.
DISCUSSION: Early indications suggest that VNS is safe and acceptable in PWS. Preliminary findings as to efficacy will be presented at the conference, with final findings expected by the end of 2010. Efficacy of this novel treatment would lead to a full trial and may be of enormous benefit to people with PWS.

28. ARE THERE DIFFERENCES BETWEEN PEOPLE WITH PRADER-WILLI SYNDROME AND HEALTHY CONTROLS IN HEART RATE VARIABILITY PARAMETERS IN RESPONSE TO EATING-RELATED PICTURES?

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INTRODUCTION: The analysis of heart rate variability (HRV) is a well validated and world-wide accepted non-invasive technique for the assessment of autonomic nervous system (ANS) activity. The ANS is composed of two pathways: the sympathetic and parasympathetic trunks. It provides the organism with a highly efficient regulatory system which is able to flexibly adapt the functioning of the body's organs, the so-called vegetative processes, to environmental changes and challenges. Thus the ANS plays a central role as the most important regulatory system for health and well-being of an individual as well as for the ability to deal with and tolerate stress. HRV is based on permanent changes in the speed of the heart beat and uses successive beat to beat intervals of the electrocardiogram (ECG). HRV can be determined by two different measures, namely the time domain and frequency domain analysis. Of special interest are frequency-related parameters since they allow measure activity of the sympathetic (low frequency band, LF) and parasympathetic (high frequency band, HF) nervous system. Until today, only a few studies have dealt with HRV activity in PWS patients, and they came to different conclusions. Therefore, the purpose of this study was to examine sympathetic and parasympathetic responses of PWS patients, especially when they are confronted with eating-related pictures.
METHODS: 38 PWS patients (23 males, 15 females, mean age = 28.7 years) were compared to 29 healthy controls matched for gender and age. 2 patients with uniparental disomy did not show any pathological HRV findings. ECG was recorded from the four standard electrode positions during three measurement intervals: 5 minutes during a resting condition without any stimulation, 5 minutes while participants were shown 17 pictures of chairs as neutral stimuli and 5 minutes while they were shown 17 pictures with delicious dishes. Data were analyzed by a two-factorial analysis of variance with the factors "group" and "condition" as the factor of repeated measurement.
RESULTS: In general, there exist significant group differences in some time- and frequency-related parameters. Out of the many HRV variables LF- and HF-parameters are of special interest. Comparing responses between conditions, PWS patients showed stronger LF-responses and lower HF-responses to the eating-related stimuli. These differences were not as pronounced in healthy controls.
DISCUSSION: As could be expected, PWS patients show high sympathetic responses in HRV parameters while at the same time parasympathetic activity is reduced. This result indicates that eating-related situations are strong stressors for PWS patients. To our knowledge this is the first study in the relevant literature which directly examined ANS activity in PWS during eating-related confrontations.

29. POLYSOMNOGRAPHY IN ADULT OBESE SUBJECTS WITH AND WITHOUT PRADER-WILLI SYNDROME

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INTRODUCTION: Normally, obese subjects have an increased fat free mass when compared to lean subjects. Obesity associated with Prader-Willi syndrome is usually characterised by a lower fat free mass and a reduced muscular tone. Patients with Prader-Willi syndrome (PWS) are at risk of a variety of abnormalities of breathing during sleep, such as obstructive and central sleep apnea (OSAS) and abnormal ventilatory responses to hypoxia and hypercapnia. We studied a group of adult PWS subjects who performed complete sleep studies compared to a group of non Prader-Willi syndrome obese subjects matched for sex, age and BMI selected from the data base of our Laboratory of Sleep Diseases.
METHODS: 9 PWS patients, 8 del15 and 1 UPD, 4 females and 5 males, aged 28.9 ± 3.4 SD years with a BMI of 46,21 ± 6.9 SD, and 9 matched non Prader-Willi syndrome obese subjects, aged 31.4 ± 4.6 years with a BMI of 48,5 ± 6,7, were recruited for the study. All patients underwent an adaptation night and then a full-night polysomnography (PSG). Parameter registered were EEG EOG; ECG; respiratory effort by thoracic and abdominal strain gauges, nasal air-flow, snoring nose, oxyhaemoglobin (SaO_2) using a pulse oxymeter with finger probe; Macrostructure of sleep analysis (Sleep Stages) according to Rechtschaffen and Kales' criteria was performed. Respiratory parameters included: apnea/hypopnea index (AHI), basal oxygen saturation (basal SaO_2), lowest oxygen saturation (lowest SaO_2), % time spent at oxygen saturation below 90%, average minimum SaO_2 during desaturations.
RESULTS: AHI was significantly different ($p<0.05$) between the two groups (9,5 ± 7,8 SE of PWS patients vs 43 ± 10,6 SE of non Prader-Willi syndrome obese subjects). So 4 PWS patients (2f/2m) were positive for OSAS, instead all the non Prader-Willi syndrome obese subjects were positive for OSAS, 5 of them with a high AHI (> 30). Concerning the saturimetric variables only basal SaO_2 was significantly different ($p<0.05$) between the two groups (92,4% ± 1,0 SE of PWS patients vs 87,1% ± 1,4 SE of non Prader-Willi syndrome obese subjects). All the other saturimetric variables of non Prader-Willi syndrome obese subjects were lower than that of PWS patients even if they were pathologic in both groups.
CONCLUSIONS: Our PWS patients seem to confirm the slight positiveness of OSAS known in the scientific literature, with a tendency to low saturimetric data. On the other hand, they show less pathologic polysomnographic data compared to non Prader-Willi syndrome obese subjects matched for sex, age and BMI. Further observations may be appropriate to confirm our results.

30. THE RELATIONSHIP BETWEEN REALITY AND FANTASY IN YOUNG PEOPLE WITH PRADER WILLI SYNDROME

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INTRODUCTION: Young children do not distinguish the difference between reality and fantasy. Gradually they improve, becoming fully aware of this distinction at the age of eight (J.Piaget). Research was carried out to understand the tendency of people with PWS with reference to this topic.
METHOD: Sample: 7 patients aged 10 to 12 years (First group), 10 patients aged 18-25 years (Second group). Data were drawn from parents' reports.
RESULTS OF THE FIRST GROUP: 4 subjects showed, in the ordinary daily experiences, stubborn behaviour that suggested they were unable to distinguish objective facts from those they imagined; they often resorted to telling lies reflecting their truths which contrasted with reality.
RESULTS OF THE SECOND GROUP: 7 subjects showed that, in ordinary daily routine, they could tell the difference between reality and fantasy; in 2 cases subjects appeared overcome by imagination, with objects and facts acquiring meanings completely different from reality, provoking uncontrolled emotional reactions; a similar delirious behaviour was shown by a third subject, for a short period, after a traumatic experience.
DISCUSSION: The results in the greater part of the first group, being unable to distinguish between reality and imagination, suggest they were probably still in the phase normally belonging to children younger than 8 years. Their mental retardation could be responsible for this delay. In the second group the results indicated that almost all subjects have overcome children's confusion between reality and fantasy. In a few cases they showed that the relationship between reality and imagination was deeply deteriorated: they were dominated by delirious thoughts and reactions.
RESULTS: The results suggest that it is important that parents, teachers and caregivers understand whether the confusion shown by people with PWS between reality and imagination is due to a temporary evolutionary phase, or is a symptom of a psychiatric disturbance.

31. RELATIONSHIP BETWEEN PEOPLE WITH PWS AND THEIR SIBLINGS: PARENTS REPORT

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INTRODUCTION: When a child is affected by chronic disease the relationship between siblings is influenced by the family's attitudes. On this issue we carried out a research study.
METHODS:. Sample, 52 siblings aged 8-44 years (M=16 years). Siblings of 39 patients with PWS aged 6-36 (M=14 years). Data collected through a specific Parents' Questionnaire (P.Q.) and reports drawn during Parents' Groups (P.G.)

RESULTS: P.Q. Knowledge of the syndrome varied widely: 98% of siblings know the name, 65% its main characteristics. Information source: 98% parents, 14% internet, 4% doctors, 2% conferences/association. Siblings involvement in the healthcare of their sibling with PWS: 81% show interest, the oldest ask parents for more information. Siblings' daily participation: 84% in food management (often with an authoritative attitude that increases with age). Brothers tolerate misbehaviour from their affected sibling less than sisters, reacting with verbal aggressiveness. Siblings' attitudes toward their friends: 54,9% never feel uncomfortable with their sibling having PWS.
Positive correlation was found between siblings' aggressiveness and discomfort.
Negative correlation was found between siblings' discomfort and time with their sibling with PWS and their friends.
RESULTS P.G.: siblings' jealousy and frustration were brought into light. Adolescent siblings, older than their sibling with PWS, felt deeply disturbed by their sibling's misbehaviour in public.
DISCUSSION: The results of the P.Q. and the P.G. show different perceptions of this issue. The findings of the P.Q. reflect rational optimistic attitudes. According to parents, more than half of the siblings never feel uneasy spending time with their friends and the child with PWS; they collaborate in their sibling's involvement and care; when siblings get older they change role from playmate to parent-substitute. The results of P.G. bring out the inner emotional, often painful, implications in the relationship between siblings and the person with PWS; parents understand that adolescent siblings may see their social image damaged by misbehaviour of the person with PWS. The support of the group allows parents to face the most difficult aspects of this issue.

32. INTERPERSONAL RELATIONSHIPS AMONG ADULTS WITH PRADER-WILLI SYNDROME RESIDING IN GROUP HOMES

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INTRODUCTION: Many adults with PWS now reside in group homes due to the need for environmental structure and support to manage the food-related behaviors associated with the syndrome. As a result, the expected life span has increased and the quality of life has improved for people with PWS. Yet the nature of interpersonal relationships among people with PWS has not been described. It has been reported often that deficits in social skills among people with PWS lead to behavioural problems. There are 58 adults with PWS living in group homes at Regens Wagner Absberg, Germany. Supervising this program has provided the opportunity and experience to observe interpersonal relationships among persons with PWS. In addition to the phenotypic behaviours associated with the syndrome, there are unique and recognizable characteristics of behavioural interaction affecting the relationships among PWS-persons, between PWS-persons and others with developmental disabilities, and between PWS-persons and staff.
METHODS: Anecdotal experience from a supervisory perspective is derived from direct contact with PWS-persons individually, in therapeutic groups, and from observed or reported social experiences involving PWS-persons and their support staff.
RESULTS: The interpersonal relationships among PWS-persons are often characterized by poor real quality of relationship and weak continuity; there are almost no long-term friendships among their peers. In the PWS group homes, it has been observed that there is a lot of competition about privileges or social status. Further, story telling to impress others and endless discussing and arguing are very common. Often, the poor ability to manage conflict or to use problem-solving strategies leads to escalation of behaviour with temper outbursts, aggression or self-injury. The relationships of PWS-persons to persons with other disabilities are characterized by profit orientation, e.g. to get food or money. PWS-persons often try to reach a dominating position in the relationships, e.g. by applying pressure with verbal aggression. Also, PWS-persons tend to avoid relationships with stronger people who have other disabilities. In their relationships to staff, PWS-persons demand a lot of attention, persevere to routines, and search for limits by provocation. They try to influence staff for their own interests, and they show strong fixations on persons of authority.
DISCUSSION: This report represents the first effort to define the nature of interpersonal relationships among persons with PWS living together in group homes. Among these 58 PWS-persons living at Regens Wagner Absberg, the observable deficits in social skills leading to interpersonal conflict were egocentrism, inability to delay personal needs, poor problem solving strategies, poor self-reflection abilities, and a poor ability to talk about their emotions, problems or needs. Additional factors influencing the quality of interpersonal relationships of people with PWS in a negative way are difficulty with perspective taking, language problems, intellectual deficiency, impaired judgment, autistic tendencies, compulsive behaviour, and weak control over frustration, aggression and emotions. It is hypothesized that lack of opportunity or unfavourable experiences with peers in childhood results in social isolation during the developmental period, and this has a strong and lasting deleterious effect on relationships in adulthood. Future interventions focusing on these social skill deficits in PWS-persons might improve their capacity for making and sustaining meaningful interpersonal relationships.

33. PERSONS WITH PWS HAVE RESEMBLANCES TO AND DIFFERENCES FROM PERSONS WITH ASPERGER SYNDROME. ARE THE RESEMBLANCES FROM AUTISTIC TRAITS?

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Comparison between specific clinical features of PWS and Asperger syndrome is presented in 86 persons with PWS and in several with Asperger syndrome in addition to those reported in the literature, especially by Wing L, Gillberg C and Attwood T.

1. Resemblances to Asperger syndrome: extreme egocentricity and difficult interacting with peers, immaturity with regard to feelings, delayed social maturity and social reasoning, limited vocabulary to describe expression of emotion, difficulty with the mutual communication, all or none thought, desire for monopolization, impaired memory processing, very good long term memory, remarkable knowledge in an area of interest, tendency to be pedantic, tendency to persecution complex, liability to have OCD, strictness about breaking one's promise with him/her, making a fool of the peers and sibs out of high pride, clumsiness of motor coordination, hyposensitivity to pain and /or temperature, etc.

2. Differences from Asperger syndrome: sensitivity to facial expression of others, most behaviors for providing pleasure rather than to overcome anxiety or providing relaxation, food as the common special interest, feeling sympathy and expressing consolation, usual prosody, no idiosyncratic use of words, usually no repetitive patterns of speech, no idiosyncratic vocalization but with high pitch and metallic, fascination with food with unusual intensity or focus (stuck on food), vivid imagination but making up likely stories, convincing and prompt lying with theory of mind, great dog fancier, usually good at maintaining in class, no dietary sensitivity but tendency to choose food with high energy, no unusual gait besides with hypotonia and/or obesity, normal sensitivity to sounds, impulse control disorder especially to food, etc.

Most features of PWS resembling those of Asperger syndrome were considered to be caused by social developmental delay and some other impairment of brain function rather than by autistic traits.

34. AUTISM AND PRADER-WILLI SYNDROME: LITERATURE REVIEW AND THE BASIS OF A RESEARCH PROJECT

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INTRODUCTION: Research on specific brain dysfunctions in autism has encouraged further research to increase knowledge and improve therapeutic practices. There is an increasing interest in syndromes with a known aetiology which overlap with the autistic syndrome. Chromosomal abnormality in the region 15q11-q13, involved in Prader-Willi syndrome (PWS), is now most often found in autistic syndromes. Phenotypic similarities between these 2 syndromes are reported in the literature.
METHODS: A preliminary study was conducted among 13 PWS patients followed in the French reference center for PWS to evaluate for clinical signs of autism that these patients present. The CARS, the Vineland and the CBCL were used.
RESULTS: Even if the first results are in line with the data in the literature, none of the patients encountered presented a clinical picture that could lead to a diagnosis of autism. However, many similarities further encourage us to compare these two pathologies. Indeed, recently published studies have shown that specific brain structures, necessary for the understanding of social codes, present abnormalities in subjects with autism and with PWS. Until now no studies of brain imaging, looking for anomalies specific to these difficulties, have been conducted in children with PWS. We have developed a protocol whose objective is to study the phenotypic similarities, to collect clinical data and to explore any cerebral abnormalities through morphometric imaging studies with MRI and PET in patients with PWS and with autism. These data will be compared subsequently to look for correlations. We will carry out various statistical analyses, group analyses and correlation analyses with the clinical data. All clinical scores will be used as a covariate in the model analysis with SPM2.
CONCLUSION: This research protocol will improve knowledge of the neural basis of disorders of social interaction like PWS from a common genetic model of autism syndrome.

35. DEMENTIA IN A WOMAN WITH PRADER-WILLI SYNDROME

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INTRODUCTION: Compared to people without intellectual disabilities ageing specific conditions occur more often and, in general, they appear earlier in life. Dementia is one of these ageing specific conditions. Persons with Down syndrome are known to have an increased risk to develop dementia of Alzheimer type. Less attention has been paid, however, to the risk of dementia in other specific genetic syndromes associated with ID like PWS. We report on a 58-year-old woman with Prader-Willi syndrome (PWS) and dementia.
METHOD: The clinical characteristics of this woman will be presented. Decline in functioning was measured on the SRZ and VABS scale. Characteristics of dementia were measured using the DSDS. Possible differential diagnoses were excluded.
RESULTS: Functional deterioration on all domains of the SRZ and VABS was assessed. Scores on the DSDS were indicative for the presence of dementia in the very late stage.
DISCUSSION: This case report illustrates a new research area in older adults with PWS. Dementia might be associated with PWS. In the case of dementia, more clinical studies are warranted to observe whether premature Alzheimer changes or indications of other dementia forms are more prevalent in people with PWS.

36. TREATMENT OF RECTAL PICKING BEHAVIOR IN PWS WITH SENSORY STIMULATION

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INTRODUCTION: It is estimated that skin picking behavior occurs in 2/3 of people with PWS. Rectal (anal) picking is less common and may be associated with chronic stress. There are anecdotal reports indicating variable success when using sensory integration methods to treat skin picking in PWS. The authors report on the treatment of a young man with PWS who displayed rectal picking that was chronic (several months duration) and severe (recurrent bleeding with self-induced rectal prolapse requiring emergency room treatment two to three times per day). This study is the first to document the successful use of a scheduled, non-contingent, sensory stimulus to treat rectal (anal) picking behavior in a naturalistic setting.
METHODS: Anecdotal experience, literature review, and single case design with treatment intervention in a naturalistic setting inform this report. Data collection was supervised by the author[1].
RESULTS: A functional analysis of behavior identified the activities and time of day when rectal picking behavior occurred. Several methods of sensory stimulation were offered to the man, and he selected the use of a back roller. Treatment sessions of three to five minutes each were scheduled four times daily during times when rectal picking was most likely to occur. Additional interventions were required to accommodate this treatment: extra staff, an increase in the density of scheduling mutually selected activities, and a transient increase in antipsychotic medication. After four weeks of intervention, there was a decrease in intensity and severity of rectal picking. After six weeks of intervention, episodes of self induced rectal prolapse stopped. After eight weeks of intervention, the frequency of rectal picking episodes was significantly reduced. Psychotropic medication was tapered and discontinued, and participation in community activities was gradually restored. After one year, the man abruptly refused the intervention. He resumed daily, severe rectal picking for one week at which point he consented to resume the sensory intervention. This was followed by a dramatic reduction in picking, and his remission has been sustained for over four years.
DISCUSSION: The skin picking behavior associated with PWS can be understood as a habit disorder (mindless, self-soothing, repetitive action). When it is associated with self-injury, it is usually a manifestation of an impulse control disorder that worsens with stress. Faulty feedback mechanisms in PWS perpetuate behaviors such as rectal picking. In PWS pain is not a deterrent to picking because sensory neurons in the dorsal lateral spinal pathways conveying pain are diminished. Although picking elicits a profound, negative response from the caregiver, the individual with PWS rarely experiences disgust that might deter the behavior. A scheduled, non-contingent, sensory experience was an effective treatment for reducing rectal picking behavior in this case. Staff tolerance, consistency and perseverance were essential to this man's recovery.