Canadian Pediatric Endocrine Group

2008 Scientific Meeting

Thursday - Saturday

April 3-5, 2008

Pacific Palisades Hotel

1277 Robson Street
Vancouver, BC

CPEG
GCEP

UBC

Welcome

Dear Delegates,

I am delighted to welcome delegates and speakers to the 2008 Scientific Meeting of the Canadian Pediatric Endocrine Group / Groupe Canadien d'Endocrinologie Pédiatrique (CPEG/GCEP) in Vancouver. This year it is especially pleasing that we are renewing our longstanding collaboration with our pediatric endocrine nursing colleagues who are members of Canadian Pediatric Endocrine Nurses / Infirmieres Canadiennes D'Endocrinologie Pediatriques (CPEN/ ICEP).

Your feedback from the 2007 meeting has been noted and implemented in this year's meeting. The organizing and scientific committee have designed an exciting program encompassing novel aspects of pediatric endocrinology and diabetes, spanning basic science and clinical practice. This meeting offers attendees a unique opportunity to advance knowledge, network with colleagues and share experiences.

I am confident that you will also enjoy the social program which as always includes 'endocrine' entertainment. The meeting is also structured to afford time to access the many attractions offered in downtown Vancouver.

I would like to thank all those who have assisted in organizing this meeting including the organizing and scientific committee, local planning group and our sponsors. Your feedback and support is always welcomed.

Enjoy the meeting!

Cheril Clarson, FRCP(C)
President, CPEG, 2007-2009

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Program Organizing and Scientific Committee

Robert Barnes, Jean-Pierre Chanoine, Cheril Clarson, Sheila Kelton, Daniele Pacaud, Dina Panagiotopoulos, Zubin Punthakee, Diane Wherrett

Local Organizing Committee

Jean-Pierre Chanoine, Kristina Hiemstra, Sheila Kelton

Learning Objectives

1. Identify cholesterol and beta cell dysfunction in type 2 diabetes
2. Present cell therapies for diabetes
3. Review of mechanisms of beta cell apoptosis in diabetes
4. Review of continuous glucose monitoring in diabetes
5. Update current knowledge of onset puberty and use of aromatase inhibitors in precocious puberty
6. Identify mechanisms of growth hormone induced insulin resistance
7. Overview of testicular function in pediatric cancer survivors
8. Review of advances in management of diabetes insipidus

Credits

This event is an Accredited Group Learning Activity as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Canadian Paediatric Society. (12.25 hours)

Biographies

Dr. C. Bruce Verchere

Bruce Verchere is a Professor in the UBC Departments of Pathology & Laboratory Medicine and Surgery, head of the Diabetes Research Program at the Child & Family Research Institute at the BC Children's & Women's Health Centre, and the inaugural Irving K Barber Chair in Diabetes Research. He has a PhD from the UBC Dept of Physiology (1991), pursued fellowship training in diabetes research in Seattle and Geneva, and returned to Vancouver in 1997. His research aims to understand how pancreatic islet beta cells function and why they are killed or are dysfunctional in both type 1 and type 2 diabetes and in transplanted islets.

His research group at BC Children's Hospital is funded by grants from the Canadian Diabetes Association, the Juvenile Diabetes Research Foundation, and the Canadian Institutes of Health Research. He was co-recipient of the UBC Outstanding Young Alumnus Award (2000), is a Senior Scholar of the Michael Smith Foundation for Health Research (2006), and was awarded the Canadian Diabetes Association Young Scientist Award (2006). Dr. Verchere has been active on a number of grant review panels, including the CIHR Metabolism panel, as Chair of the Personnel Awards Committee for the Canadian Diabetes Association (CDA), and is currently Co-Chair of the Juvenile Diabetes Research Foundation Group II Islet Biology and Transplantation Committee. He is also co-chair of the Canadian Diabetes Association Clinical & Scientific Session National Conference in 2007 and 2008.

Dr. Timothy J. Kieffer

Dr. Kieffer obtained his Ph.D. in the Department of Physiology at the University of British Columbia and then conducted postdoctoral training at Harvard Medical School and Massachusetts General Hospital. He then took up his first faculty position at the University of Alberta before moving back to Vancouver, where he is now a Professor in the Departments of Cellular and Physiological Sciences, and Surgery. His Laboratory of Molecular and Cellular Medicine is focused on developing novel strategies to treat diabetes using gene- or cell-based approaches. He currently sits on Editorial Boards for Physiological Reviews and the Canadian Journal of Diabetes and has received scholarships from MSFHR, AHFMR, CDA and JDRF.

Dr. James D. Johnson

Jim Johnson is an Assistant Professor in the Department of Cellular and Physiological Sciences and the Department of Surgery at the University of British Columbia. Dr. Johnson is a graduate of Lakehead University and obtained his Ph.D. from the University of Alberta before receiving post-doctoral training at Washington University in St. Louis with Drs. Kenneth Polonsky and Stan Misler. An expert in beta-cell biology and signal transduction, he is the author of over 35 peer-reviewed articles since 2000, many in top journals. He holds grants from the Juvenile Diabetes Research Foundation, the Canadian Institutes of Health Research, the Canadian Diabetes Association, the Natural Sciences and Engineering Research Council, the Stem Cell Network, and the Canada Foundation for Innovation. Dr. Johnson holds the prestigious international Career Development Award from the Juvenile Diabetes Research Foundation, as well as Scholarships from the Canadian Diabetes Association, the Michael Smith Foundation for Health Research, and the Canadian Institutes for Health Research.

Dr. Bruce Buckingham

Bruce Buckingham, M.D. is a Professor at Stanford University and Packard Children's Hospital. Dr. Buckingham received his MD from the University of California at San Diego, and his Pediatric Endocrinology training at the Children's Hospital of Los Angeles.

Dr. Buckingham's research interests have focused on continuous glucose monitoring in children. He is Principal Investigator at Stanford for DirecNet, an NIH sponsored multicenter study group which evaluates continuous glucose sensors in children. This group has conducted a number of studies over the last 6 years assessing the accuracy, function and utility of the Minimed CGMS sensor, the GlucoWatch, and the Therasense Navigator. His current work focuses on the use of continuous glucose sensors in real-time, and the development of a closed-loop for management of persons with type-1 diabetes and in pediatric intensive care units. These efforts are being funded by the JDRF.

Dr. Mark Palmert

Mark Palmert moved to the Hospital for Sick Children in September 2007. At SickKids, he is Head of the Division of Endocrinology, a Senior Associate Scientist in the Genetics and Genome Biology Program within The Research Institute, and an Associate Professor of Paediatrics at the University of Toronto.

Mark graduated from the Medical Scientist Training Program at Case Western Reserve University with an MD and PhD in 1992 and then completed his paediatrics residency, chief residency and endocrinology fellowship training at Children's Hospital, Boston. He was on staff in Boston until 2001 when we returned to Cleveland (2001-2007) to join the Endocrinology faculty at Rainbow Babies and Children's Hospital and the Pediatrics and Genetics Departments at Case Western' s Medical School. He remained in Cleveland until his recent move to Toronto in 2007. The main focus of his clinical and basic research activity has been variations in the timing and pace of pubertal development, and he directs an active laboratory-based program designed to identify genetic factors that modulate the timing of puberty within the general population.

Dr. Leo Dunkel

Professor Leo Dunkel is currently Professor of Paediatrics at the University of Kuopio, Finland. He studied medicine at the University of Helsinki, and completed his residency in paediatrics and paediatric endocrinology at the Hospital for Children and Adolescents, University of Helsinki. After his residency for paediatrics, he was a post-doctoral fellow at Stanford University's Division of Reproductive Biology. His research interests are related various aspects of reproductive biology. Currently his research interests include topics like genetic regulation of sexual maturation, mechanisms and significance of "mini-puberty", and sex steroid mediated modulation of height growth. Professor Dunkel has been a member of ESPE since 1988 and he was a Council Member in 2000-2004. He is Director of Training for paediatric endocrinology in Finland.

Dr. Michael O. Thorner

Dr. Thorner did his medical training at the University of London and graduated MB BS with honors in Therapeuics and Applied Pharmacology in 1970. He was trained in Internal Medicine and Endocrinology and Metabolism at teaching hospitals in London before being recruited to the University of Virginia in 1977. He rose through the ranks becoming Chair of the Department of Medicine in 1997 and remained in that position until 2006 when he was appointed David C Harrison Teaching Professor of Internal Medicine devoting himself to full time research, teaching and clinical work. His research accomplishments include proposing and providing the seminal data to support primary medical treatment for prolactin secreting tumors irrespective of their size as they shrink with medical therapy. He identified a patient with a growth hormone releasing hormone (GHRH) secreting pancreatic tumor which led to the identification, characterization, purification and sequencing of this hormone. Later they cloned the receptor for GHRH.

Dr. Thorner's more recent research focuses on somatopause, the decline of growth hormone secretion that occurs progressively from puberty. This decline may account for the changes in body composition that occur as a person ages and may contribute to the frailty of aging. Dr. Thorner and his colleagues have also investigated the mechanism by which GH regulates insulin sensitivity in adipose tissue that regulates partitioning of nutrients.

Dr. Thorner and his colleagues have developed sensitive and specific assays for measurement of ghrelin, a hormone which is produced in the stomach and regulates growth hormone and appetite. These assays will help investigators understand the regulation of ghrelin, with implications for research into obesity and aging.

Dr. Thorner's team has completed a study on the effects of the use of an experimental drug that mimics ghrelin. For up to two years, growth hormone secretion can be increased in healthy older people to similar levels observed in the young—this is associated with beneficial changes in body composition including the prevention of further reduction in fat free mass (i.e. muscle) seen on placebo and, in fact, an increase in muscle mass. Further studies are needed to determine whether this will slow or prevent frailty in aging.

Dr. Steve Shalet

Professor Shalet is an honorary Consultant and Professor of Medicine and Endocrinology at the University of Manchester, UK. He completed a BSc in Physiology at London University and qualified in medicine at the Royal London Hospital. Medical training posts in London and Bristol were followed by an appointment at the Christie Hospital, Manchester, as Research Fellow in Endocrinology in 1974 and then subsequently Consultant in 1978.

Professor Shalet has extensive research interests in the late endocrine effects following treatment of cancer, pituitary disorders and in particular abnormalities of growth hormone secretion.

Previous positions and official activities include Chairman of the Strategic Planning Committee of the European Society of Pediatric Endocrinology, Co-Editor of the first edition of the Oxford Textbook of Endocrinology and a member of the Council of the Society for Endocrinology and the SAC in Endocrinology and Diabetes. Professor Shalet has served as President of the Endocrine Section of the Royal Society of Medicine, as a member of the Council of the European Society of Paediatric Endocrinology, was Chairman of the Specialist Training Committee in Diabetes and Endocrinology for the North West Region and as a member of the Clinical Practice Committee of the Society for Endocrinology.

Dr. Jack Holland

Jack Holland is Professor of Pediatrics and a full time pediatric endocrinologist at McMaster Children's Hospital. He is also Chair of the Research Ethics Board, Faculty of Health Sciences McMaster University/Hamilton Health Sciences.

Dr Holland graduated in Medicine from Queen's University Belfast in 1969 and completed postgraduate training in Internal Medicine, before immigrating to Canada in 1972 where he entered the Pediatric Residency programs at Kingston and Toronto. He undertook addition research training at the University of California at San Francisco in pediatric endocrinology, and returned to Canada in 1977 to a Faculty position at the University of Toronto and the Hospital for Sick Children.

From 1991 until 2001 he was appointed Chair of the Department of Pediatrics at McMaster University. He is a Past President of the Canadian Paediatric Society and of Healthy Generations, the Foundation of the Canadian Paediatric Society. His clinical and research interests are in disorders of growth and puberty.

Dr. Josephine Ho

Dr. Ho obtained her medical degree at the University of Western Ontario (London, Ontario) and then completed her pediatric residency and pediatric endocrine and metabolism fellowship at the University of Calgary (Calgary, Alberta). She also recently completed her MSc in epidemiology at the University of Calgary. Currently, she is practicing as a pediatric endocrinologist at the Alberta Children's Hospital (Calgary, Alberta) and has an appointment as an assistant professor at the Faculty of Medicine, University of Calgary.

Dr. Daniel G. Bichet

Dr. Daniel G. Bichet took his medical training in France (M.D. University of Besançon) then at the University of Montreal, McGill and the University of Colorado Medical Center where he was a fellow with Dr Robert W. Schrier.

He has been investigating the molecular and cellular basis of hereditary polyuric states since the early 90's and, together with Michel Bouvier at the University of Montreal, proposed a pharmacological chaperone treatment for misfolded mutations responsible for X-linked Nephrogenic Diabetes Insipidus. More recently, with Alan Peterson (McGill), he has generated a unique Avpr2 GFP-LacZ reporter mouse line with an expression pattern reflecting the expression program of the endogenous Avpr2 gene.
Together these themes are aimed to provide early identification and new treatments for hereditary polyuric states.

Dr. Scott A. Rivkees

Scott Scott Rivkees M.D. is Professor of Pediatrics and Associate Chair for Research at the Yale University School of Medicine. Dr. Rivkees is a graduate of Rutgers University and the University of Medicine and Dentistry of New Jersey. He received postdoctoral training in Pediatric Endocrinology at Massachusetts General Hospital and Harvard Medical School. He has authored more than 175 reports, including original articles, chapters, editorials and books. He is the Editor-in-Chief of the Journal of Pediatrics Endocrinology and Metabolism. He is Chair of the Lawson Wilkins Pediatric Endocrine Society Public Policy Committee. He is a member of the Federal Affairs Committee of the American Thyroid Association. He also works with the US Senate Childrens and Families Subcommittee on legislative issues.

Thursday, April 3, 2008

12:30 Registration open, exhibits open

13:30 Opening Remarks & Welcome
Dr. Jean -Pierre Chanoine, Dr. Cheril Clarson and Nicole Kirouac

13:45 Split rooms, Nurses: Business meeting
(in the Merenge)

Split rooms, MDs

Theme 1: Diabetes: from Basic to Clinical

Moderator: Dina Panagiotopoulos

13:45 Cholesterol and Beta Cell Dysfunction in Type 2 Diabetes: Knowing Your ABCs
Dr. C. Bruce Verchere, Vancouver, BC

14:30 Cell Therapies for Diabetes
Dr. Timothy Kieffer, Vancouver, BC

15:15 Refreshment break, exhibits open

15:45 Theme 1 Cont'd, Mechanisms of Beta-cell Apoptosis in Rare and Common Forms of Diabetes
Dr. James D. Johnson, Vancouver, BC

16:30 Continuous glucose monitoring in children with type 1 diabetes/Closed loop
Dr. Bruce Buckingham, Stanford, CA

17:15 Adjourn

18:00 Reception, exhibits open

Friday, April 4, 2008

7:30 Breakfast buffet opens
(served in the Flamenco room, but please bring your food into the ballroom)

8:00 Business Meeting "AGM" incl. breakfast

10:00 Refreshment break, exhibits open

10:30 Split rooms, MDs: Fellow presentations (see page 11 for the schedule)
Moderator: Ralph Rothstein

Split rooms, Nurses: Growing Up Transgendered (please refer to the one page program)

12:30 Lunch served in the Art and Soul Gallery, seating in the Zin Restaurant and dessert will be served in the exhibit area

Theme 2: Growth and Puberty
Moderator Jean-Pierre Chanoine

13:30 Why does Jill Start Puberty at 9 and Jane at 12? Genetic Investigation of Variation in Pubertal Timing
Dr. Mark Palmert, Toronto, ON

14:15 Aromatase Inhibition and Male Puberty
Dr. Leo Dunkel, Kuopio, Finland

15:00 Refreshment break, exhibits open

15:30 Theme 2 Cont'd, Mechanisms of GH-induced Insulin Resistance
Dr. Michael Thorner, Charlottesville, VA

16:15 Testicular Function in Cancer Survivors and Testosterone
Dr. Steve Shalet, Manchester, UK

17:00 Adjourn

18:30 DINNER at Dockside Restaurant and evening program.

Complimentary shuttle bus service will be available between the Pacific Palisades Hotel and the Dockside Restaurant at 6:00PM and 6:30PM. To ensure your seat on the bus, please sign up at the meeting registration desk to indicate which departure time you prefer.

Saturday, April 5, 2008

7:30 Breakfast (served in the Zin Restaurant), exhibits open

8:30
Theme 3: Debate: Should Pediatric Patients Participate in Clinical Research?
Moderator: Diane Wherrett
Dr. Josephine Ho – (Con side), Calgary, AB
Dr. Jack Holland – (Pro side), Hamilton, ON
(15 Presentation each, 5 min rebuttal each, 20 min discussion)

9:30 Fellow presentations Cont'd (see page 11 for schedule)

10:00 Refreshment break, exhibits open

Theme 4: Water Metabolism
Moderator: Dan Metzger

10:30 Advances in Diabetes Insipidus
Dr. Daniel Bichet, Montreal, QC

11:15 The Management of Central Diabetes Insipidus in Infancy: Desmopressin, Low Renal Solute Load Formula, Thiazide Diuretics
Dr. Scott A. Rivkees, New Haven, CT

12:00 Presentation of Dr. John Bailey Fellow Research Award

12:15 Closing remarks

12:20 Adjourn

Fellow Presentations Schedule

Friday, April 4, 2008

10:30 A Randomized Placebo-Controlled Trial of Zoledronic Acid for the Treatment of Osteopenia in Children and Adolescents with Crohn's Disease
(AM Sbrocchi et al)

10:45 Medication Induced Diabetes during Treatment of ALL: Prevalence and Risk Factors in a Population of Patients at the Hospital for Sick Children
(Dror Koltin et al)

11:00 Appetite-Related Hormone Levels in Patients with Craniopharyngioma and Hypothalamic Obesity
(Clodagh S O'Gorman et al)

11:15 Growth Hormone Treatment in Prader-Willi Syndrome: A Single Centre Experience
(*Tammie Dewan et al)*

11:30 Promoter Haplotype in Insulin-Like Growth Factor-Binding Protein-3 (IGFBP3) gene: Correlation with Serum Levels, Growth and Response to Growth Hormone Treatment in Short Children Born Small for Gestational Age (SGA)
(*D.C.M. van der Kaay et al)*

11:45 Risperidone and Diabetes Mellitus in Childhood
(Patricia Olivier et al)

12:00 Predictors of DM Hospitalizations Following the Transition to Adult Diabetes Care
(Meranda Nakhla et al)

12:15 Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE): An Unusual Case of Late Development of Metastases Presenting with Severe Hypercalcemia
(B. Wicklow et al)

Saturday, April 5, 2008

9:30 Hypothyroidism and Autism combined with Pseudohypoparathyroidism in the Absence of Albright's Hereditary Osteodystrophy and GNAS Imprinting Changes: A Novel Clinical Syndrome?
(Teresa Pinto et al)

9:45 Ontogeny Of Preproghrelin, Ghrelin, Obestatin And Prohormone Convertase In Rat Pancreas And Stomach
(*Pallavi Walia et al)*

Abstracts

A Randomized Placebo-Controlled Trial of Zoledronic Acid for the Treatment of Osteopenia in Children and Adolescents with Crohn's Disease

AM Sbrocchi[1], CJ Rodd[2] and S Forget[3].
[1]Pediatric Endocrinology, Montreal Children's Hospital, Montreal, QC, Canada H3H 1P3;
[2]Pediatric Endocrinology, Montreal Children's Hospital, Montreal, QC, Canada H3H 1P3 and [3]Pediatric Gastroenterology, Montreal Children's Hospital, Montreal, QC, Canada H3H 1P3.

Introduction
Children with Crohn's disease often have poor bone mineral density (BMD), which can lead to fractures. In adults, bisphosphonates are used to treat glucocorticoid-induced osteoporosis. Studies on bisphosphonates in children are limited, and have not been performed in pediatric patients with Crohn's disease. This study assesses the safety and efficacy of a single infusion of zoledronic acid in pediatric patients with Crohn's disease and osteopenia.

Methods
Patients aged 6-18 years (y) with Crohn's disease and osteopenia were randomly assigned to either receive a single infusion of zoledronic acid (0.066 mg/kg, maximum of 4 mg), or intravenous saline as placebo. Use of prednisone, immunosuppressors, nutritional status, pubertal status, level of physical activity and disease severity were recorded. Patients were followed for 1 year. The primary outcome was change in z-score lumbar spine (LS) BMD measured by DXA 6 months (m) after treatment. Secondary outcomes included change in LS BMD at 12 m, change in total body BMD, urine markers of bone turnover, and side effects.

Results
A total of 13 pubertal patients were recruited (9 males (M), 4 females (F), mean age 15.1y, mean disease duration 3.5y) and all had adequate calcium and vitamin D intake for a minimum of 6 m prior to enrolment. Seven patients received zoledronic acid (5M, 2F, mean age 15.5y) and 6 received placebo (4M, 2F, mean age 14.6y). Results are presented in the table. Side-effects were mild and included fever, arthralgia and nausea (3/7 treated, 3/6 placebo). There was no significant difference in LS BMD z-scores between groups at baseline, however LS BMD z-score increased significantly at 6m in the treated group ($p = .02$), but not in the placebo group ($p = .15$).

Table 1

	Zoledronic acid		Placebo	
Time	Baseline	Post	Baseline	Post
z-LS BMD	-2.34	-1.90*	-2.68	-2.30

Paired t test, * = $p = 0.02$

Conclusion
A single infusion of zoledronic acid significantly increases LS BMD in pediatric patients with Crohn's disease and osteopenia, and was well tolerated.

Medication Induced Diabetes during Treatment of ALL: Prevalence and Risk Factors in a Population of Patients at the Hospital for Sick Children.

Dror Koltin[1], Lillian Sung[2], Ahmed Naqvi[2], and Stacey L. Urbach[1,2]

The Division of Endocrinology[1], and Hematology/Oncology[2], The Hospital for Sick Children, Toronto, Ontario.

Background: Medication induced diabetes (MID) occurs in 11% - 30% of patients receiving chemotherapy for acute lymphoblastic leukemia (ALL). Older age, obesity, family history of diabetes and trisomy 21 are risk factors for MID. Most cases of MID occur during induction chemotherapy in ALL. However, factors associated with the development of MID specifically during induction have not been clearly described.

Objectives: To describe the prevalence and course of MID and to determine factors associated with MID during induction chemotherapy in pediatric ALL.

Methods: Patients treated for B precursor or T-cell ALL at The Hospital for Sick Children between 1998 and 2004 were identified. Their medical charts were retrospectively reviewed to estimate the prevalence and describe the course of MID (defined as 2 or more blood glucose values $\geq$ 11.1 mmol/L) during induction chemotherapy. Associations between the presence of MID and demographic and treatment variables were assessed.

Results: 373 patients were diagnosed with B precursor or T-cell ALL during the study period. 56 patients (15%) developed MID, 11 of whom (20%) received insulin. Patients who developed MID were more likely to be older than 10 years at diagnosis (OR = 10.7, 95% CI = 5.6 – 20.2), have a higher BMI (OR 1.2, 95% CI = 1.1 – 1.3), have CNS disease at diagnosis (OR 3.2, 95% CI 1.4 – 9.1), be treated with a 4 drug induction (OR 5.9, 95% CI 2.9 – 11.9), and have trisomy 21 (OR 3.7, 95% CI 1.1 – 11.6). On multivariate analysis, age over 10 (OR 11.6, 95% CI 6.0 – 22.6) and CNS disease at diagnosis (OR 4.2, 95% CI 1.2 – 14.2) remained significantly associated with MID.

Conclusions: Patients older than 10 years of age and those who have CNS disease at diagnosis are more likely to develop MID. Puberty, associated with increased insulin resistance, may explain in part the association between age and MID. The etiology behind the association between CNS disease and MID is not clear.

Appetite-Related Hormone Levels in Patients with Craniopharyngioma and Hypothalamic Obesity

Clodagh S O'Gorman[1], Judith Simoneau-Roy[1], Paul Pencharz[2], Khosrow Adeli[3], Jill Hamilton[1].
Divisions of [1]Endocrinology, [2]Gastroenterology & Nutrition, [3]Clinical Biochemistry, Department of Pediatrics, The Hospital for Sick Children, Toronto.

Background: Hypothalamic obesity occurs commonly following treatment for pituitary or hypothalamic tumors, including craniopharyngioma (CP). The literature evaluating satiety hormones in this population is sparse. Ghrelin, secreted by the stomach, is implicated in satiety, with ghrelin reduction following oral food intake. Ghrelin is reduced in obesity. Studies suggest that ghrelin reduction after OGTT is less in obese than lean children.

Objectives: To compare several dynamic and other fasting appetite hormone levels in response to OGTT in adolescents with CP and age- and weight-matched obese controls(C).

Methods: 31 obese patients were recruited: 16 CP; 15 C. Exclusion criteria included chronic illness or medications that alter glucose homeostasis. All patients had fasting bloodwork (glucose, ghrelin, PYY, adiponectin, leptin, insulin) and standard 120 minute 75g OGTT (ghrelin sampled at 30 and 60 minutes).

Results: Background characteristics were similar between groups. Mean age (years) was 15.5 ± 4.0 CP and 15.1 ± 2.3 C (p 0.77) and mean BMI (kg/m^2) 5.2 ± 8.0 CP and 33.5 ± 4.9 C (p0.47). From baseline to 30 minutes during OGTT, ghrelin reduction (pmol/L) was significantly less in CP (-43.4 ± 38.8 v -70.8 ± 35.8, $p < 0.05$) but from baseline to 60 minutes, ghrelin reduction was not statistically different (-73.1 ± 47.6 v -83.3 ± 48.0, p 0.57). Leptin, PYY and adiponectin were non-significantly higher in CP.

Discussion: Our study suggests that ghrelin falls more after OGTT in patients with exogenous obesity than in weight-matched CP patients. It is unclear whether this post-prandial ghrelin reduction causes or is caused by appetite suppression. Furthermore, it is unclear whether it is *absolute* or *change* in ghrelin that impacts appetite. Ghrelin dynamics in response to oral glucose load differ between obese CP and controls, with an apparent delayed reduction in ghrelin in CP patients at 30 minutes, but with no difference at 60 minutes. These differences may be due to hypothalamic damage or alterations in neural-enteral feedback mechanisms.

Growth Hormone Treatment in Prader-Willi Syndrome: A Single Centre Experience

Tammie Dewan, Laura Stewart, Ralph Rothstein, Jean-Pierre Chanoine
Endocrinology and Diabetes Unit, British Columbia Children's Hospital, University of British Columbia, Vancouver BC

Prader-Willi Syndrome (PWS) is characterized by hypotonia and failure to thrive in infancy followed by obesity and short stature beginning in early childhood. Growth hormone (hGH) is approved in the US for PWS and improves growth, body composition and motor development. Sleep apnea testing is recommended prior to initiating therapy, as an association has been found between hGH treatment and sudden death in subjects with PWS, likely due to worsening of obstructive sleep apnea.

The goal of this study was to describe our experience with hGH treatment in patients with PWS.

We performed a retrospective chart review of 11 subjects (3M:8F) with genetically proven PWS. We anayzed growth parameters (CDC growth charts) at baseline and during the longest follow up period up to one year, IGF-1 and fT4 before and after initiation of hGH, and the results of pituitary hormone testing and sleep studies.

Median (range) age at the time of hGH initiation was 1.33 (0.42-13) yrs. Dose of hGH was 0.24mg/kg/week (range 0.18-0.3) and treatment duration 2.3 (0.25-9) yrs. Two subjects were GH deficient (peak GH response <8 ng/ml on 2 stimulation tests and decreased height velocity, hGH dose 0.18 mg/kg/week). Nine received hGH based on PWS diagnosis (0.3 mg/kg/week). One 7 year-old boy decreased BMI by 4.2 kg/m^2 during the first 2 years of treatment.

Table: Anthropometric measures before and during hGH treatment

Mean (range)	Before hGH	During hGH
Weight SDS	-0.9 (-3.8 to 2.1)	-0.3 (-2.3 to 2.0)
Weight SDS	-1.8 (-4.1 to 1.1)	-0.8 (-3.1 to 1.5)
BMI/weight for length SDS*	0.7 (-1.2 to 3.8)	0.8 (-2.1 to 3.1)

*: weight for length up to 3 yrs and body mass index [BMI] after 3 yrs of age

Pre-treatment IGF-1 levels were normal in 10/11 subjects. Growth hormone at the dose of 0.3 mg/kg/week led to supraphysiological values of IGF-1for age and sex. Three subjects had hypothyroidism. Six subjects underwent a sleep study prior to treatment (5 N and one with central apnea).

In conclusion, hGH increased height and weight SDS but did not affect BMI SDS (except in one subject). hGH was well tolerated. The long-term implications of supraphysiological IGF-1 levels in PWS subjects receiving hGH are unknown.

Promoter Haplotype in Insulin-Like Growth Factor-Binding Protein-3 (*IGFBP3*) gene: Correlation with Serum Levels, Growth and Response to Growth Hormone Treatment in Short Children Born Small for Gestational Age (SGA)

D.C.M. van der Kaay[1,2,3], A.C.S. Hokken-Koelega[1,2], A.E.J. Hendriks[1], S.W. de Kort[1], R.H. Willemsen[1], W. Ester[1], R.W.J. Leunissen[1], J.R. Paquette[3] and C.L. Deal[3]. [1]Pediatric Endocrinology, Erasmus Medical Center, Rotterdam [2]Dutch Growth Foundation, Rotterdam, The Netherlands, [3]Endocrine Service, Sainte-Justine Hospital Research Center, Montreal, Canada.

Background
IGF-I and IGFBP-3 levels are low in SGA children with height <-2.5 SDS. The -202 A/C and -185 C/T SNPs are located near elements involved in directing *IGFBP3* promoter activity and expression. Changes in promoter CpG methylation status affect transcription factor binding and transcriptional activation of *IGFBP3 in vitro*.

Objectives
To 1) assess the relationship between *IGFBP3* promoter SNPs, IGFBP-3 levels and growth in short prepubertal SGA children (n=289), 2) evaluate the usefulness of both SNPs in predicting growth response to GH treatment, 3) assess promoter methylation status (bisulfite sequencing) in short young adult SGA patients, compared to controls (n=10 samples; 10 clones/sample).

Results
Gestational age was 36.3±3.9w, birth weight -2.3±1.1SDS and birth length -3.1±1.4SDS. Baseline age was 7.0±2.4y, height -3.0±0.6SDS, fat mass -1.9±2.3SDS and IGF-I and IGFBP-3 levels were -1.2±1.3SDS and -1.3±1.1SDS, respectively. At baseline, IGFBP-3 levels were highest in patients with -202 AA genotype and decreased in patients with 1 or 2 copies of the C-allele (P<0.001). Patients with CC^{-202}/CC^{-185} haplotype, compared to patients with AA^{-202}/CC^{-185} haplotype, had lower IGFBP-3 levels (-1.8SDS vs -1.0SDS, P<0.001) and were shorter (-3.3SDS vs -2.9SDS, P=0.03). During GH treatment, patients with CC^{-202}/CC^{-185} showed a significantly greater increase in IGFBP-3 SDS and in height SDS than patients with AA^{-202}/CC^{-185}, resulting in similar IGFBP-3 levels after 6m and similar height SDS after 2y of GH treatment.

Multiple regression analysis	**Δ height SDS during the first year of GH-treatment**	
Variables	**β**	**P-value**
Δ IGFBP-3 SDS	0.11	<0.0001
Target height SDS	0.14	0.02
Δ IGF-1 SDS	0.006	0.03
Age	-0.004	0.06
Haplotype	0.15	0.09
Baseline height SDS	-0.02	0.58
R^2		0.58
Adjusted R^2		0.52

CpG methylation patterns showed more methylation of CpGs involved in transcription factor binding (Sp1, p53, USF) in short SGA patients compared to controls.

Conclusion
Polymorphic variation in the *IGFBP3* promoter region is correlated with IGFBP-3 levels and with spontaneous growth in short SGA children. Haplotype is a valuable predictor of growth response during GH treatment. Preliminary data show that an epigenetic level of gene regulation could contribute to the lower IGFBP-3 levels in short SGA cohorts.

Risperidone and Diabetes Mellitus in Childhood.

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BACKGROUND: A relationship between abnormal glucose metabolism and the use of atypical antipsychotic drugs has been clearly demonstrated in adults. Olanzapine is the drug which is most commonly implicated, with an estimated risk of diabetes increased by 5.8 times (95% CI: 2.0-16.7) compared to that observed in subjects not on antipsychotics. Risperidone is also linked to hyperglycemia, but the risk is much lower (risk of diabetes increased by 2.2 times (95% CI: 0.9-5.2). However, in the pediatric population, data corroborating these findings are sparse. So far, there are 3 long-term open-label trials of risperidone (n = 688 children) in which only one case of diabetes has been reported; therefore, diabetes does not seem to be a common complication of risperidone therapy in children.

CLINICAL PRESENTATION: At the diabetes clinic of the CHU Sainte-Justine, we identified 3 patients who were on risperidone treatment when diabetes was diagnosed:

	Patient 1	**Patient 2**	**Patient 3**
Age	13 9/12 years	8 3/12 years	12 6/12 years
Sex	Male	Male	Male
BMI	16.3 (10th perc)	21.0 (>95th perc)	15.3 (5th perc)
DKA	No	No	Yes
Familial type 2 DM	+ (Paternal aunt)	-	-
Anti-GAD (U/mL)	29.00	<1.00	7.1 (N<1.0)
Other diagnoses	-Encephalopathy of unknown origin -Obsessive compulsive disorder	-Autism -Seizures	-Congenital rubella -Seizures -Encephalopathy
Other medications	Dexamphetamine, quetiapine (PRN)	Carbamazepine, Venlafaxine, Clonidine	Valproic acid
Risperidone	1.5-1.0 mg	0.5 mg HS (x 12 months)	1.5 mg HS

DIAGNOSIS: It is not clear what kind of diabetes is precipitated by the use of atypical antipsychotics. In our patients, there is great heterogeneity. *Patients 1* and *3* presented with elevated anti-GAD antibodies. *Patient 2*, who presented with a high BMI and absence of anti-GAD Ab, which may have been evocative of type 2 diabetes, is still insulin dependent despite having ceased risperidone therapy. *Patient 3* may have "multifactorial" diabetes because of congenital rubella, a condition known to be associated with diabetes.

CONLUSION: Risperidone can cause endocrine complications in pediatric patients, such as hyperprolactinemia, weight gain and thyroid disorders, but also hyperglycemia and diabetes. With regards to diabetes, the pediatric population presents both the gender imbalance and the absence of relation to the dose of antipsychotic reported in adults. Therefore, it is important to identify and better characterize these patients with abnormal glucose metabolism on risperidone therapy to improve our comprehension of this entity.

Predictors of DM Hospitalizations Following the Transition to Adult Diabetes Care

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During transition to adult healthcare many adolescents with diabetes (DM) are lost to follow-up. However, few studies have documented which factors, including models of transition, are associated with better health outcomes.

Our objectives were to 1) describe rates of DM-related hospitalizations (DKA and hypoglycemia) after transition to adult care and 2) assess the association of method of transition to DM hospitalizations.

We used health administrative data including the Ontario Diabetes Database to identify our cohort and outcomes, and a survey all of the pediatric diabetes centers in Ontario (5 tertiary and 29 secondary centers) about their modes of transition. All young adults prevalent with DM for >5 years by age 16 years between 1996 and 2002 were assigned to the nearest diabetes centre. Outcomes were DM hospitalizations from ages 18-20 years. Transition methods were grouped into those in which new physicians and health care teams were involved in ongoing care versus those in which some elements of care remained constant.

Among the 1507 young adults, DM hospitalization rates increased from 153/1000 patients in the 2 years prior to, to 190/1000 in the 2 years after transition ($p=0.03$). Prior DM hospitalizations between age 16-18 years ($p<0.01$), lower SES ($p<0.01$), female gender ($p=0.02$) and lower physician supply ($p=0.02$) were predictive of increased DM hospitalizations after transition. After controlling for all other factors patients who were transitioned to a new physician and allied health care team were more likely to be hospitalized than those who had continuity with at least part of the team (RR 1.64, $p=0.01$).

Female gender, previous DM hospitalizations, lower SES and lower physician supply were predictive of DM hospitalizations after transition. Methods of transition to adult care that include continuity with some part of the pediatric health care team were associated with fewer DM hospitalizations after transition. These data have important implications in planning transition programs for youth with DM.

Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE): An Unusual Case of Late Development of Metastases Presenting with Severe Hypercalcemia

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Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE) is an extremely rare thyroid tumor characterized by a proliferation of spindle cells and presumed to be of thymic origin. We describe an adolescent boy whose SETTLE tumor was diagnosed retrospectively after he presented with lung metastases and severe hypercalcemia of malignancy.

Our patient initially presented at 4 years of age with a painful right thyroid nodule. Following hemithyroidectomy pathology revealed a well circumscribed, non-encapsulated tumor consisting of mature cartilage, neuroglial, mucinous, respiratory and gastric mucosal tissues, and a nodule of spindle cells of undetermined nature. A cervico-thyroidal teratoma was diagnosed. He received no further treatment and remained stable at follow-up to 3 years post-operatively.

Nine years later he presented to emergency with fever, productive cough, pleuritic chest pain and shoulder pain. Chest CT revealed multiple bilateral pulmonary nodules. CT scans of the head, neck, and abdomen, and whole body bone scan were negative. Total and ionized serum calcium measured 3.08 mmol/L (2.20-2.62) and 1.75 mmol/L (1.15-1.38), serum phosphate was 0.87 mmol/L (1.06-2.00) and serum PTH was <0.1 pmol/L. PTHrP measured 24.8 pg/ml (0-15). Despite hyperhydration, furosemide and subcutaneous calcitonin, the hypercalcemia worsened and a single dose of pamidronate was given. Lung biopsy pathology revealed a malignant proliferation of highly mitotic spindle shaped cells. No teratomatous elements were seen. Re-examination of the spindle cell nodule from the original thyroid specimen revealed similar pathological features and a diagnosis of primary thyroid SETTLE tumor with lung metastasis was made. Now 7 months post diagnosis, this 14 year old boy is undergoing chemotherapy with some decrease in tumor burden.

To our knowledge this is the first description of PTHrP-related hypercalcemia associated with a SETTLE tumor in an adolescent boy. This report adds to the limited literature available concerning this rare tumor.

Hypothyroidism and Autism combined with Pseudohypoparathyroidism in the Absence of Albright's Hereditary Osteodystrophy and *GNAS* Imprinting Changes: A Novel Clinical Syndrome?

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Introduction and Aim: Pseudohypoparathyroidism (PHP) typically arises from defects in *GNAS* (20q13.3), an imprinted gene locus with multiple transcriptional units. Recent studies have shown that the mutations responsible for the PHP-Ib form, affect control elements regulating the imprinting of *GNAS*. The purpose of this report was to describe an apparently novel form of PHP-Ib in two brothers with unique clinical features.

Clinical Report: The male propositus presented at 12 years with increasing seizure frequency and autism. Investigations suggested PHP: (Ca^{2+} 0.9 mmol/L, N: 1.1-1.3; PO_4 1.8 mmol/L, N: 1.0-1.7; PTH 54 pmol/L, N: 1.1-6.8). PTH infusion test (Parathar 3 units/kg) demonstrated only a 6-fold increase in $_u$cAMP (N: >10-fold increase) and a 2.5% reduction in percent tubular reabsorption of phosphate (N: 5-16% reduction). Trans-ilial bone biopsy revealed increased cancellous bone volume (38% above the average) with a 4-fold elevation in bone formation rate. These results confirmed renal resistance to PTH with bone tissue responsiveness. TSH resistance was also suspected: TSH 6.7 mU/L; FT4 <5 pmol/L, TRH stimulation consistent with primary hypothyroidism, negative anti-thyroid antibodies and lack of a goiter. An older brother also manifested autism, PTH resistance and primary hypothyroidism in the absence of positive anti-thyroid antibodies; however, a large goiter was present. Southern blot analyses using gDNA from the propositus and methylation sensitive restriction enzymes showed no evidence of a methylation defect in *GNAS* exon A/B. Analysis of genomic DNA from the affected children and their parents through microsatellite markers located centromeric and telomeric of *GNAS* and through single nucleotide polymorphisms within the *GNAS* locus, showed that the two affected individuals inherited different parental alleles.

Conclusions: We describe two brothers with autism, primary hypothyroidism and PHP, where the genetic and epigenetic findings suggest that *GNAS* is not linked to this form of PHP-Ib. This constellation of features may represent a novel clinical syndrome.

Ontogeny Of Preproghrelin, Ghrelin, Obestatin And Prohormone Convertase In Rat Pancreas And Stomach

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Ghrelin (GHR) is mainly secreted by the stomach in adults. In contrast, in the perinatal period, the pancreas is a major source of GHR while stomach GHR concentrations increase progressively with age. GHR (aa 24-51) results from the posttranslational processing of preproghrelin (PPG, 117 aa) by prohormone convertase 1 (PC1). PPG is also predicted to generate obestatin (aa 76-98). In pancreas, proinsulin is processed by PC1 and PC2 and proglucagon mainly by PC2. We compared the ontogeny of PPG, GHR, obestatin, PC1 and PC2 in the rat. Stomach and pancreas were collected in SD rat embryos (E21) and neonates (PND1, 6, 13, 21 and 28) (n = 7/gr). We examined the localization of GHR (2 different antibodies) with PPG, obestatin, PC1, PC2 (stomach and pancreas) and with insulin and glucagon (pancreas) by double immunofluorescence (IF) and in situ-hybridization (ISH).

Results. In stomach, PPG(+) cells were abundant from E21 (similar results for IF and ISH). In contrast, GHR cells were rare at E21 and their absolute and relative number increased to PND28. All GHR(+) cells were also PPG(+). Obestatin and PC1 colocalized only with PPG(+)/GHR(+) cells and increased progressively from E21 to PND28. PC2 was not found in stomach. In pancreas, in contrast to the stomach, there were only a few PPG(+) cells in the periphery of the islets at all ages and each PPG(+) cell was also GHR(+), obestatin(+) and PC1(+). None of the GHR(+) cells colocalized with insulin but we observed both GHR(+)/glucagon(-) and GHR(+)/glucagon(+) cells. Only the GHR(+)/glucagon(+) cells were also PC2(+).

Conclusions. 1. In both stomach and pancreas, all GHR(+) cells were also PPG(+)/obestatin(+), suggesting that each PPG molecule generates both hormones; 2. the excess of PPG(+)/GHR(-)/obestatin(-) cells in the stomach suggests that the low level of PC1 expression in early days determines the low PPG processing to GHR/obestatin; 3. In pancreas, the presence of PC2 in GHR(+)/glucagon(+) cells but not in the GHR(+)/glucagon(-) cells supports the existence of 2 distinct GHR cell types.

Immunostaining for PPG, GHR and Obestatin in Perinatal Rat Stomach:

Age (days)	E21	PND1	PND6	PND13	PND21	PND28
PPG(+) (cells/field)	167 (48)	155 (56)	132 (30)	158 (46)	403 (43)	347 (36)
GHR(+)/Ob(+) (cells/field)	1 (0)	2 (0)	4 (1)	7 (2)	20 (7)	29 (3)
% of PPG(+) cells that are also GHR(+)/Ob(+) cells	0.7 (0.2)	1.2 (0.7)	2.8 (0.8)	4.3 (1.3)	5.2 (1.9)	8.4 (1.1)

Mean (SD), $P < 0.001$ (ANOVA) for each variable

NOTES