

IPWSO 10th International conference, Havana, Cuba

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Clinical and Scientific conference: Speaker abstracts

I. Genetics, Epigenetics & Animal Models

I-1. Invited Talk: “Genetics in PWS: Where We Have Been and Where We are Going”

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Prader-Willi syndrome (PWS) is a complex contiguous gene syndrome involving multiple imprinted loci within chromosomal region 15q11.2-q13. Loss of the paternally expressed *SNORD116* locus is a major contributor to the phenotype, but multiple other genes within the region that are only paternally expressed also contribute to the phenotype.

There are 3 main genetic mechanisms (molecular classes) for PWS: paternal deletion, maternal uniparental disomy (UPD) 15, and imprinting defect. Within each molecular class there are subclasses. Approximately 90% of the deletion class can be accounted for by type 1 and 2 deletions, but 10% are atypically sized deletions which can impact the phenotype.

DNA methylation analysis can diagnose >99% of all cases of PWS, but it cannot determine the molecular class. Therefore, it is a powerful screening tool for PWS, but once the diagnosis of PWS is established the molecular class needs to be determined for genotype-phenotype correlation and genetic counselling purposes. DNA methylation is also available for prenatal diagnosis and for newborn screening. Mosaic imprinting defects and mosaic trisomy 15 with maternal UPD 15 are underdiagnosed conditions.

The exact role and targets of the PWS imprinted genes is an area of active research. Also, the role of the upstream exons of the *SNURF-SNRPN* locus is currently not clear. Some genes elsewhere in the genome are emerging as targets of the PWS imprinted loci and will be discussed. Gene therapy may have a role to play in the treatment of PWS in the future.

I-2. Invited Talk: “An Update on Mouse Models of PWS”, the Zafgen lecture

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Over 25 spontaneous and targeted mutations affecting imprinted genes at the orthologous mouse PWS locus have been reported. This long list includes mutations that target individual PWS genes, as well as large deletions and imprinting center mutations that inactivate multiple PWS genes. These mutants have provided important insights into the inheritance and pathogenesis of PWS. Although many PWS traits have been modeled by existing mice, to date no single mouse model recapitulates all traits commonly seen in individuals with PWS. The presentation will highlight select mouse models that replicate salient PWS traits, as well as traits that have not been well replicated in mice. With a few notable exceptions, PWS mice have had limited use as preclinical models with which to assess the efficacy of new therapeutics. Such studies have been hindered by insufficient phenotypic characterization, heterogenous assessment methods, and inadequate knowledge of the translatability of human phenotypes into animal read-outs. An initiative by the PWS mouse models community to address these preclinical needs will also be described.

II. Endocrinology

II-1. Invited Talk: “Oxytocin in Prader-Willi Syndrome”

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Oxytocin (OXT) is a neuropeptide that plays an important role in modulating social interactions and mother-infant bonding. Quantitative neuroanatomical studies of postmortem human hypothalamic tissue from patients with Prader–Willi Syndrome (PWS) have demonstrated a reduced number and volume of OXT neurons in the paraventricular nucleus in comparison with controls. Similarly, an alteration in the OXT system was described in PWS mouse models. In patients with PWS increased levels on circulating levels have been documented.

After the first study we published in 2011 using OXT in adults with PWS¹ several clinical trials have been implemented administering OXT in children, adolescents and adults with PWS^{2,3,4}. All but one study reported positive effects on behavior albeit the effect on eating behavior is poor and the main effect of OXT remained to be defined. Only one study showed negative results in adolescents and adults with a worsening of temper tantrums particularly with high doses of treatment. Additional clinical trials are ongoing in children and adolescents.

One proof of concept study was performed in infants with PWS showing positive effects on oral and social skills⁵ therefore recapitulating the effects observed in the mice model with MAGEL2 deficit. Therefore, OXT in this period of life may be of unique interest by improving the first nutritional phase including increasing appetite and oral motor skills decreasing social withdrawal and improving mother-infant interactions. Most importantly is the change of connectivity of the orbitofrontal cortex observed in brain fMRI after OXT treatment in infants with PWS. Neurons of this brain region is known to be involved in feeding regulation and social stimuli-responsive neurons. This is online with the correlations observed between brain changes and changes on oral and social skills. Long term effect of OXT treatment after 3-4 years documented the good tolerance of an early short course of oxytocin and in communicating skills. It remains to document the effect vs placebo, to find the best dose and duration of the treatment before using it in routine in neonates and infants. That will be done in a further international clinical trial which will start soon. Moreover, OXT may have a role in brain plasticity early in life but seems to also display a physiological role and may be useful afterwards.

Interestingly induced pluripotent stem (iPS) cells differentiated into neurons are useful tools to understand the effect of OXT in neurons. Indeed, it has been possible to show impaired prohormone processing in these neurons driving OXT deficit⁶.

In addition, OXT and ghrelin both impaired in PWS are functionally linked. Indeed, administration of OXT modifies circulating ghrelin levels in infants. OXT and ghrelin G protein coupled receptors may form heterodimers that modify the effect of OXT⁷. Both OXT and ghrelin play a role in controlling appetite and behavior and both hormones are used in ongoing clinical trials in PWS. Therefore, the challenge will be to identify the specific and possibly complementary role of these two hormones and their use in PWS.

Special thanks to Prader-Willi France Association, Foundation for Prader-Willi Research (FPWR), Lejeune Foundation, Groupama Foundation and the French Ministry of Health for funding projects on oxytocin.

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II-2. Invited Talk: “An Overview of Endocrinology in Adults with PWS”, the Levo Therapeutics lecture

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Introduction: Many symptoms in Prader-Willi syndrome (PWS) are similar to symptoms caused by insufficient hormone levels. In this presentation symptoms and treatment of growth hormone deficiency, central adrenal insufficiency, central hypothyroidism and hypogonadism in adolescents and adults with PWS will be discussed.

Muscular hypotonia, abnormal body composition and low energy expenditure are well-known symptoms of growth hormone deficiency (GHD). Available knowledge suggests some degree of GHD in adults with PWS and studies have consistently shown significant benefits of GH therapy on body composition, physical and psycho-social function in adults with PWS. GH might increase the risk for type 2 diabetes, and glucose levels should be monitored during GH treatment.

Adrenal insufficiency is characterised by fatigue, weight loss and insufficient response to stress and central adrenal insufficiency was hypothesized to be responsible for sudden deaths in PWS. However, most studies indicate that hypocortisolism is rare, and evaluation and treatment only necessary when clinically indicated.

Increase in weight, lethargy and low body temperature are characteristics of hypothyroidism. Central hypothyroidism has been reported with a high frequency in children but not in adults. Due to similarities with symptoms in PWS regular follow-up of thyroid function is recommended.

Sex hormones are important for appearance of body gender, body composition, bone mineral density, fertility and quality of life. Primary hypogonadism is most frequent in PWS but there is a continuum from complete primary hypogonadism to complete central hypogonadism. There is no consensus on management of hypogonadism in PWS and an individual consideration of benefits and risks with sex-hormone treatment is recommended. Inhibin-B, a marker of fertility, is undetectable in most adults with PWS. Five pregnancies have been described in PWS women. Fertility in PWS males has not been reported.

Conclusions: Some symptoms in adults with PWS share similarities with hormone insufficiencies. As some of the hormone insufficiencies are common, diagnosis and hormone replacements are important along with prevention of obesity and treatment of comorbidities for optimal care in adults with PWS.

II-3. “Central adrenal insufficiency is rare in adults with Prader-Willi syndrome”

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Introduction: Prader-Willi syndrome (PWS) is associated with deficiencies of several hypothalamic-pituitary hormones. Central adrenal insufficiency (CAI) has been reported in PWS with prevalences ranging from 0% to 60%, depending on endocrine testing methods, cut-off values and population studied (pediatric vs adult). It has been speculated that CAI might be responsible, at least in part, for the high mortality (3% a year across all ages) in patients with PWS. If CAI is present, timely diagnosis and treatment is needed to prevent avoidable mortality. There are no guidelines on the appropriate evaluation and management of CAI in adults with PWS. Many patients with PWS receive standard hydrocortisone (HC) treatment around periods of physical and/or psychological stress. As the behavioural phenotype of PWS includes temper outbursts, this may lead to frequent HC administration by caregivers, at least in adults. Frequent administration of HC increases the risk of obesity, hypertension, osteoporosis and diabetes, already major problems in adults with PWS. It is therefore of utmost importance to assess the real prevalence of CAI in order to prevent both under- and overtreatment with HC.

Methods: The hypothalamic-pituitary-adrenal axis was tested in 71 adult subjects (55 Dutch, 10 French, 6 Swedish) with genetically confirmed PWS. Multiple dose metyrapone (MTP) test was performed in 45 subjects and insulin tolerance test (ITT) in 26 subjects. When levels of 11-deoxycortisol (S) during MTP were greater than 230 nmol/L (7.6 g/dL) or levels of cortisol during ITT were greater than 500 nmol/L (18.1 µg/dL), adrenal insufficiency was excluded. Additionally, we collected medical files of 630 adult patients with PWS from Italy (240), France (110), the Netherlands (106), Australia (60), Spain (45), Sweden (38) and the United Kingdom (31), which we recognize may not represent the entire PWS population. We reviewed these files for data on previous surgery and/or health problems related to hypocortisolism.

Results: Data on 71 adult subjects (41 males and 30 females), median age (range) 26.3 yr (18.0 – 55.5), median BMI (range) 28.7 kg/m² (20.0 – 58.2), with genetically confirmed PWS were collected. 31 subjects (44%) were using GH treatment since childhood. At MTP test, all 45 subjects had S ≥ 230 nmol/L. At ITT, all subjects had cortisol levels ≥ 500 nmol/L, apart from one subject who had a peak cortisol level of 494 nmol/L. Although this is still within measurement error for the cortisol assay, this patient was prescribed HC for use during physical stress. Even patients with a low baseline cortisol level (lowest: 102.0 nmol/L) had normal MTP or ITT test results. Both tests were tolerated well by all individuals. None of the 630 patients who had undergone surgery or infections without peri-operative or illness-associated HC treatment developed hypocortisolism.

Conclusions: CAI is rare (1.4%) in adults with Prader-Willi syndrome. Because of the low probability for CAI we recommend dynamic testing for hypocortisolism only when clinically indicated. Routine prescription of HC stress medication is not necessary.

II-4. “Systemic Inflammation and The Effect of a GLP-1 Receptor Agonist in Adults with Prader-Willi Syndrome”

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Introduction: Prader - Willi syndrome (PWS) is one of the most common known genetic obesity disorders, and is associated with a reduced life expectancy due to cardiovascular disease. Increased systemic low-grade inflammation is postulated as a contributor, despite reported lower visceral fat mass and increased insulin sensitivity in PWS. In non-syndromic obesity, GLP-1 receptor agonist therapy is thought to decrease cardiovascular morbidity and mortality by reducing low grade inflammation; however, its effects have not been studied in PWS. This project aimed to assess immune cell activation markers and circulating cytokine profile, fasting and postprandially, in PWS compared to lean and adiposity-matched obese subjects. Further, to determine the acute effect of a GLP-1 receptor agonist on immune cell activation and circulating inflammatory cytokines in PWS.

Methods: Baseline and postprandial levels of immune cell activation markers were quantified via flow cytometry, and inflammatory cytokine levels measured via ELISA in 9 PWS adults and compared with 11 adiposity-matched obese and 10 healthy lean subjects. In a single-blinded, crossover design, PWS and obese subjects received either a single dose of 10 mcg exenatide (Byetta) or normal saline subcutaneously 15 minutes before consuming a standardised 600 kCal meal.

Results: PWS subjects demonstrated increased fasting and postprandial innate immune cell activation, with significantly higher expression of granulocyte and monocyte cell markers. A single dose of exenatide with a meal yielded significant decreases in innate immune cell activation markers in PWS and obese subjects. Circulating cytokines E-selectin, MIC-1 and PAI-1 were elevated in PWS compared to lean but not different to obese. sICAM-1 levels were not different between the groups. IL-6 was higher in PWS than in Obese and Lean. A single dose GLP-1 receptor agonist did not significantly lower IL-6 response postprandially.

Conclusions: We found evidence for low grade systemic inflammation in PWS, with elevated expression of innate immune cell activation markers and serum IL-6 levels. The increased IL-6 levels fasting and post-prandially appears to be specific to PWS and merits further investigation regarding its possible contribution to the cardiovascular risk. A single dose GLP-1 receptor agonist appeared effective in reducing postprandial immune cell activation, but without IL-6 suppression. Currently running investigations will examine the long-term effects of GLP-1 receptor agonists on systemic inflammation in PWS.

III. Gastrointestinal & Nutrition

III-1. Invited Talk: “Comprehensive Overview of Digestive Issues in Prader-Willi Syndrome”

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Nutrition and digestive issues are commonly encountered in the management of Prader-Willi syndrome with impacts upon the lifespan. This presentation will involve a summary of existing published literature relevant to digestive related issues in Prader-Willi syndrome including data from clinical practice and research studies performed on gastrointestinal emptying/motility, impact of dietary interventions upon behavior, impact of GI issues upon morbidity/mortality in Prader-Willi syndrome and preliminary data from gut microbiome analyses in Prader-Willi syndrome.

III-2. “Review of Short and Long-Term Outcomes of Bariatric Procedures in Prader-Willi Syndrome and Other Hyperphagic Disorders”

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Introduction: Morbid obesity is an increasing concern throughout the developed and developing world with rising prevalence and anticipated significant utilization of healthcare resources over the next several decades. As there has been suboptimal results from lifestyle interventions and pharmacologic approaches to date, bariatric surgical and endoscopic procedures have increased over the past 2 decades including adolescents and children with significant post-operative improvement in weight related co-morbidities. As weight management strategies are most challenging among those with hyperphagic disorders, we chose to review published outcomes of bariatric procedures among individuals with hyperphagic genetic and acquired disorders including Prader-Willi syndrome (PWS), Melanocortin-4-Receptor Mutations (MC4R), Bardet-Biedl syndrome (BBS) and Hypothalamic Obesity (HO).

Methods: Review of existing published literature using the following search terms: Prader-Willi syndrome, Bardet-Biedl syndrome, hyperphagia, bariatric surgery, MC4R/melanocortin-4-receptor mutations, hypothalamic obesity, bariatric procedure. Information collected included demographics, genetic testing (if available), anthropometry, type of procedure, long-term outcomes and complications. Given the rarity of the disorders, case series and clinical reports were included in the analyses. Publications were carefully reviewed to minimize duplicity of data. Post-surgical outcomes were compared with outcomes of other large bariatric cohorts (e.g. LABS, Teen-LABS). T-test, Mann-Whitney, Chi-Square and Fisher’s Exact Test were used for data analyses (Graph Pad Prism[®] version 6.05).

Results: A total of 49 publications were identified (32-PWS, 8-MC4R, 5-BBS, 4-HO). A total of 163 adults and children with history of bariatric procedures were described with variable duration of follow-up. Procedures performed included jejunioileal bypass, gastric bypass, vertical band gastropasty, adjustable gastric band, biliointeric balloon (BIB), biliopancreatic diversion and sleeve gastrectomy. 117 (72%) patients with PWS, 31 (19%) patients with MC4R mutations, 7 (4%) with BBS, 8 (4%) with HO. Mean ages for procedures: HO 18.25 years, BBS 30.2 +/-9.6 years, MC4R 29.4 +/-14.6 years, PWS 19.4 +/-6 years. Variable improvement in weight-related co-morbidities was reported (PWS sleeve data: OSA resolved in 21/24 PWS vs teen sleeve patients ($p=0.053$), similar improvement in hypertension ($p=0.68$) and dyslipidemia ($p=0.76$ vs Teen LABS sleeve patients). There were higher rates of weight regain among patients with PWS with history of biliopancreatic diversion ($p=0.01$), and gastric bypass ($p<0.0001$) in comparison to other obese patient cohorts. Among patients with MC4R mutations, there appear to be higher rates of long-term weight regain among patients with homozygous mutations in comparison to those with heterozygous mutations in the MC4R receptor. Complications included weight regain requiring reoperation/revision, infections, adhesions/band slippage, nutritional issues (osteopenia, anemia) complications, including some deaths due to infection or gastric perforation with higher rates of complications associated with some procedures including BIB ($p<0.001$).

Conclusion: Bariatric procedures have been reported among individuals with hyperphagic disorders including Prader-Wlli syndrome with varying results and higher incidence of complications. Completion of genetic testing prior to completion of bariatric procedures among those with symptoms of hyperphagia should be considered as part of preoperative evaluation. Comprehensive long-term (5 years, 10 years) outcomes data including quality of life data after bariatric procedures is needed.

III-3. “Long-acting GLP-1 agonist treatment in Prader-Willi Syndrome: Benefits on appetite, behaviour and cognition versus risks?”

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Introduction: Management of hyperphagia and behavioural problems in Prader-Willi Syndrome (PWS) remains a major challenge. GLP-1 agonists have gained traction in the treatment of diabetes in people with PWS and have potential beneficial effects on the gut and brain. However, little is known yet about the safety of this drug class in people with PWS as they can delay gastric emptying (GE). Assurance on safety is paramount to avoid potentially increasing the risk of gastric necrosis. Although still controversial, previous studies have suggested that subjects with PWS may have delayed GE. To address this, we determined GE in people with PWS compared to controls by gastric scintigraphy, the most reliable, validated method. We also assessed the gastrointestinal safety of this novel drug, which has the potential to improve appetite, behaviour and cognition in those with PWS.

Methods: In this prospective interventional study (ENGAGE PWS), GE was compared in people with PWS to lean and BMI-matched obese control individuals. All subjects had a Dual Energy X-ray Absorptiometry scan to assess body composition. Subjects with PWS who had normal GE rates were then treated with once-weekly exenatide for 12 weeks. GE was measured by gastric scintigraphy at baseline, 4 and 12 weeks, with the ingestion of 99mTc-labelled breakfast, regular blood samples and appetite assessments. For safety, treatment was discontinued in subjects with delayed GE at the 4 week assessment. All those with PWS completed the cognitive function assessment using the *Cambridge Neuropsychological Test Automated Battery* (CANTAB) and their parents/guardians completed a Hyperphagia Questionnaire (HQ) during their visits.

Results: 11 lean, 9 obese and 13 PWS aged 18-51yr were recruited. At the baseline visit, the average GE rate was similar in those with PWS compared to lean and obese controls, but we identified 3 subjects with PWS who had delayed GE and were thus excluded from the interventional study. Subjects with PWS who received weekly exenatide for 12 weeks showed a trend towards a mild delay in gastric emptying compared to baseline. Importantly, GLP-1 RA treatment had to be discontinued in 2 subjects at the 4 week visit due to delayed GE above the safety threshold. Fullness rating increased from baseline to week 4 while hunger ratings were unchanged. Weight, hyperphagia scores and cognition testing were variably affected by treatment.

Conclusions: Although we did not see an intrinsic delay in GE in most of the subjects with PWS, a proportion of subjects had significantly delayed GE and are not suitable for GLP-1 RA treatment. During treatment, we observed a mild delay in GE in most subjects, but importantly, greater effects on GE were seen in a small subset of patients. GLP-1 was well tolerated with beneficial effects on some of the subjects' weight and appetite. We recommend GE assessment before and/or during GLP-1 RA treatment for optimal safety.

III-4. “Effect of macronutrient composition on postprandial metabolism in children with Prader-Willi syndrome (PWS): preliminary findings”

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Introduction: Meals of similar caloric content but differing in macronutrient composition may impact diet-induced thermogenesis (DIT), potentially influencing total energy expenditure (TEE). Energy expended through digestion, absorption and storage of dietary protein is higher than for carbohydrate and fat. Therefore, a high-protein (HP) diet could have an influence on energy metabolism and weight control. The aim of this study was to compare the impact of a HP diet versus a typical North American, high-carbohydrate diet (standard diet) on DIT and substrate oxidation in children with Prader-Willi syndrome (PWS). Prader-Willi syndrome is a unique clinical model of childhood obesity associated with hypotonia, hyperphagia and lower metabolic rate compared to children without PWS.

Methods: Participants completed three separate study visits separated by a two to four-week washout period. Anthropometric measurements were completed at each study visit. In a randomized, crossover study design participants were randomly allocated to two isocaloric arms: a) standard diet: 55% carbohydrate, 15% protein, and 30% fat; b) HP diet: 20% of carbohydrate, 50% protein, and 30% fat. Participants received the prescribed diets (three meals plus two snacks per day accompanied by either a powder supplement (high-protein diet) or an extra snack (standard-diet) for one day prior to each study visit and a breakfast meal inside a whole-body calorimetry unit (WBCU). Diets were designed to ensure participants were in energy balance. Resting metabolic rate (RMR), DIT and respiratory exchange ratio (RER) were assessed. Differences between diets were assessed by paired sample T-test considering a significance value of $p < 0.05$.

Results: Five individuals with PWS (4F/1M, age: 14.5 ± 4.0 (11-20 years) BMI percentile: 86.2 ± 10.5 (70.2.-98.3)) were assessed. No differences were observed in the RMR (1625.5 ± 188.4 vs 1511.5 ± 168 kcal; $p = 0.49$) and DIT (200 ± 189 vs 184.3 ± 189 kcal; $p = 0.74$) measurements between HP and standard diets. However, a lower RER was observed in the HP diet in comparison to the standard diet (0.80 ± 0.2 vs 0.86 ± 0.2 ; $p < 0.009$).

Conclusion: Respiratory exchange ratio was lower in the HP diet compared to the standard diet in individuals with PWS; suggesting a shift towards fat rather than carbohydrate as a fuel source. Although no differences were observed in the DIT measurements between HP and standard diets, the small sample size does not allow for meaningful statistical considerations due to the high variation among groups. This preliminary data suggests a diet higher in protein may provide a metabolic advantage compared to a typical North American, high-carbohydrate diet. Future analysis of healthy children matched for age, sex and BMI percentile will confirm if individuals with PWS metabolize food differently as compared to healthy children.

III-5. “Relationship between Angiopoietin-like levels and non-alcoholic fatty liver disease in children with Prader-Willi Syndrome”

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Background: A recently identified liver protein, Angiopoietin-like8 (ANGPTL8), was described to be involved in different metabolic pathways related to gluco-lipid metabolism and associated with liver function and non-alcoholic fatty liver disease (NAFLD) in adult patients with Prader-Willi syndrome (PWS). This study aimed to investigate ANGPTL8 levels in children with PWS and their controls in relation with metabolic homeostasis and NAFLD.

Subjects and Methods: 29 children with genetically confirmed PWS (M/F=17/12, age 11.4±3.1y, BMI-SDS 2.4±1.2) and 29 BMI- and age-matched controls (M/F=10/19, age 12.9±3.1y, BMI-SDS 2.7±0.4) underwent analysis of serum ANGPTL8, leptin, adiponectin, glucose homeostasis, lipid profile and liver function. Fat-free mass (FFM, kg) and fat mass (%FM) were assessed by DXA, NAFLD severity by liver ultrasonography [Shannon A, *J Pediatr Gastroenterol Nutr* 2011].

Results: PWS subjects showed lower FFM (30.2±9.9 vs 39.4±13.5 kg, p<0.05) and similar %FM (45.2±6.9 vs 43.5±6.1%, ns) but healthier glucose and lipid homeostasis than controls. Adiponectin levels were higher in PWS than controls (16.2±7.8 vs 9.4±4.4 µg/mL, p<0.0001), whereas ANGPTL8 (0.50±0.29 vs 0.46±0.20 ng/mL, ns) and leptin levels (30.6±18.5 vs 30.7±15.8 ng/mL, ns), prevalence of NAFLD (55.2 vs 69.0%, ns) as well as liver function profile were similar between groups. In PWS group, ANGPTL8 levels were positively associated with BMI-SDS (p<0.05), HOMA-IR (p<0.01), leptin levels (p=0.001) and the presence of NAFLD (p<0.05), whereas in the control group they were negatively correlated with BMI-SDS (p<0.05). By stepwise multivariable regression analysis on the whole dataset, ANGPTL8 levels were independently predicted by BMI-SDS (p<0.01), leptin levels (p<0.01) and NAFLD (p<0.05).

Conclusions: Children with PWS show a healthier glucose homeostasis compared to controls. Although ANGPTL8 levels were similar between PWS and controls, our results highlight its potential role as a new biomarker of insulin resistance, liver function and NAFLD in PWS children.

IV. General Medical Issues

IV-1. *Invited Talk: “Overview and Evaluation: Infants, Children, Adolescents and Adults with PWS”*

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Introduction: During the last 2 years the CSAB has published on the IPWSO web site Overviews and Evaluation Guidance concerning Infants, Children, Adolescents and Adults. All to be downloaded: www.IPWSO.com/medical-professionals.

Background: Medical contact and services for persons with PWS varies a lot among countries, and also inside many countries. As PWS is a very complex disease, we find it important that all have regular medical evaluations, frequency depending on individual needs, for the youngest most often, older children and adults at least yearly. If not possible at a medical center with experience in PWS, it is of value that the local physicians, having not met PWS before, have access to overviews and recommendations for evaluations, that are up to date and easy to read. Families and caregivers can read and print the recommendations, and bring it with them at medical visits.

Methods: The forms are made for the mentioned four age groups, as symptoms and needs vary and change from infancy to adulthood. The overviews describe the most often met symptoms in the actual age group, and in the evaluation guidance clinical evaluation, investigations, blood tests recommended are listed. We are aware that possibilities for investigations and treatments vary from country to country and also within countries. Costs and economical support for medical services vary, but many of the recommendations especially concerning clinical evaluations and guidelines can be followed in most countries. The plan is to review the text on a regular basis, and change and add information according to the newest knowledge. Examples from the publications will be presented

Conclusion: The CSAB hope the Overviews and Evaluation guidance published can be used and found useful for both families, caregivers and medical professionals. We look forward to receiving feedback for continuing updating and bettering of the publications.

IV-2. Invited Talk: “Medical care for Patients with PWS at the National Network of Medical Genetic Services in Cuba”

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Cuba's National Program for Diagnosis, Management and Prevention of Birth Defects and Hereditary Diseases initiated in Cuba in the 80's as a comprehensive part of the country's universal health coverage, which emphasis on community-based primary care linked to secondary and tertiary care. Prader Willi Syndrome is a genetic disorder caused by deleted or unexpressed genes contained in 15q11-q13 region of paternal chromosome with ensuing disabilities.

Objective: To describe some experiences in the diagnosis and management of Prader Willi Syndrome in the National Network of Medical Genetic Services in Cuba.

Methods: a Cuban medical literature search was conducted, mainly using Pubmed and Scielo databases. A strategy was designed using mainly terms: "Prader Willi Syndrome", "Genetic services" and Cuba. The articles chosen were published in English or Spanish languages which were accessed as full texts, besides documents from the National Network of Medical Genetic Services were also checked, evaluating their contents

Results: The medical care for Prader Willi Syndrome patients was available throughout 169 municipalities, as well as provincial centers in all 15 provinces of the country, coordinated by the National Center of Medical Genetics of Cuba. Fifty Prader Willi patients were currently identified based on clinical criteria, chromosomal and molecular studies. All of them have received comprehensive medical care through genetic counseling provided by specialists of the National Health System.

Conclusions: The National Center of Medical Genetics has coordinated the medical care of Prader Willi patients and their families in Cuba allowing better prevention.

IV-3. “Incidence and Consequence of Laryngomalacia in Infants with PWS seen at Seattle Children's PWS Clinic”

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Introduction: Growth hormone (GH) is started early in infants with Prader-Willi Syndrome (PWS) to improve tone, body composition, development, and growth. Concerns about sudden death in children with PWS started on growth hormone, hypothesized secondary to worsening obstructive sleep apnea (OSA) from adenotonsillar hypertrophy, resulted in guidelines for polysomnography (PSG) evaluation before and after starting GH. We reported 2 cases of worsening OSA after starting GH thought to be secondary to unmasked laryngomalacia. Laryngomalacia in PWS is not well described but it is associated with neuromuscular disorders and it may lead to exacerbation of OSA.

Methods: A retrospective review of infants seen at the Seattle Children's PWS clinic between October 2014 and July 2019 was done. Infants who had the majority of their care done at SCH were included. Those who had sleep endoscopy with flexible fiberoptic laryngoscopy (FFL) were further reviewed for diagnosis of laryngomalacia. Descriptive statistics were done to look at incidence of laryngomalacia and obstructive sleep apnea (OSA).

Results: A total of 23 cases (7 [30%] male, subtypes: 8 [35%] deletion, 11 [48%] mUPD, 1 [4%] imprinting center defect, 3 [13%] undetermined) were reviewed. Eight (35%) were evaluated with FFL between ages 5 and 40 months old (average 13.8 ± 12.2 ; median 10) for worsening or persistent OSA or dysphagia. Out of these, 7 (88% of FFL, 30% of total) were diagnosed with laryngomalacia (2 [29%] male, subtypes: 2 [29%] deletion, 4 [57%] mUPD, 1 [14%] imprinting center defect). Of the 23 infants, 8 (35%) had worse OSA after starting GH (GH effect could not yet be determined for 6 of the 23 patients). Of these 8 patients, 4 (50%) had laryngomalacia. Four of the 8 children (50%) had adenoidectomy with or without tonsillectomy to treat the OSA. Three children had surgical intervention of the laryngomalacia and 2 of these 3 had significant improvement of OSA after supraglottoplasty.

Conclusion: OSA can lead to significant morbidity in PWS. Growth hormone may unmask underlying laryngomalacia, possibly due to improved inspiratory force, causing worsening of OSA. Laryngomalacia is not well described in this population but our infant population had a 30% incidence overall, and 88% incidence in those evaluated by sleep endoscopy. As only 35% of our patients had an evaluation with FFL, the incidence of laryngomalacia may be an underestimation. Although most infants grow out of laryngomalacia, if there are concerns of worsening OSA, then it is important to evaluate and consider treatment of this condition.

IV-4. “Increased bone density without changes in bone markers in youth with and without PWS who participated in a 24-week physical activity intervention”

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Introduction: During childhood, bone acquisition is affected by changes in hormones, height (Ht), lean mass (LM), physical activity (PA). This study compared bone mineral density (BMD), bone mineral content (BMC), and bone remodeling markers in youth with PWS versus youth with non-syndromic obesity (NSO) at baseline and after a PA intervention.

Methods: 30 boys & 24 girls participated, including 23 with PWS (Age: 11.1±2.7 y, Ht: 144.0 ±13.8 cm, LM: 29.4 ±10.6 kg, Fat: 44.8 ±10.4 %, 18 on growth hormone therapy) and 31 with NSO (Age: 9.6± 1.1 y, Ht: 147.3± 9.5 cm, LM: 33.2± 8.2 kg, Fat: 44.6± 6.2 %). Participants completed all measurements at baseline and after 24 weeks of a home-based game-centered PA intervention that included strengthening exercises twice a week. Dual x-ray absorptiometry scans of the hip, the lumbar spine (L1-L4) and full body determined BMC in g, BMD in g/cm², and body composition (facility least significant change [LSC]: hip= .020 g/cm²; spine=.030 g/cm²). Bone markers included fasting serum bone-specific alkaline phosphatase (BAP) and C-terminal telopeptide of type I collagen (CTX). Changes over time were analyzed using general estimating equations. Percent changes in bone markers were also categorized as to exceeding or not the LSC (from inter- and intra assay coefficients of variation) and compared using Chi-square analyses.

Results: There were no differences at baseline for any spine parameters between the groups (p>.050 for all); spine BMC increased from 34.87±2.08 to 37.99±2.36 g, p<.001, and spine BMD from 0.909±0.023 to 0.939±0.026 g/cm², p=.002 (LSC =.030). Hip differences between groups showed higher z-scores and BMC in NSO vs. PWS (p<.040). Hip BMD increased (0.882±0.021 vs. 0.918±0.026 g/cm²; p=.002; LSC =.020) as well as hip BMC (21.812 ±1.067 vs. 23.041±1.173; p=.012). Youth with NSO had higher BAP 139.07±6.41 vs. 108.28±9.19 U/L (p=.006) and similar CTx (2.07±0.11 vs.1.84±0.14 ng/dL; p=.193) than those with PWS at baseline. There were no group-by-time interactions for any bone marker (p>.425), or time effects (p>.209). There were no differences in the proportions of changes (pre-to-post) between the groups for BAP (12.2% increase, 61% decrease and 26.8 % no change; p=.130) or CTx (all youth: 48% increase, 36.6% decrease and 14.6% no change; p=.508). All youth gained LM (31.20±1.32 vs. 32.44±1.47 kg; p=.004) and Ht (145.7±1.6 vs. 147.9±1.8 cm; p=.002).

Conclusion: Youth demonstrated increases in bone parameters at or above the facility LSC. However, youth also increased Ht and LM, which may influence the gains in bone. During the 24-week youth PA intervention, youth participants potentially engaged in more exercises stimulating bone accrual (such as jumping and strengthening exercises); however, the lack of a control group precludes causality. In contrast to previous studies, youth with PWS had lower BAP than those with NSO; perhaps because 78% of them were on GH therapy. This study results suggest that youth with PWS can attain comparable changes in bone

parameters over six months as those with NSO. Funded by US Army Medical Research and Materiel Command W81XWH11-1-076

IV-5. “Is There a ‘Fetal Phenotype’ of Prader-Willi Syndrome?”

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Introduction: A “fetal phenotype” for Prader-Willi syndrome (PWS) has been proposed that may be identified in the third trimester of pregnancy based upon sonographic findings and maternal perception of fetal activity. Although the antenatal diagnosis of PWS has been made based upon sonographic findings, most of the findings have been described retrospectively in individuals diagnosed with the syndrome postnatally. We conducted a review of the reported findings to assess whether such a phenotype exists and may be used to identify fetuses for prenatal testing.

Methods: Perinatal data for individuals with PWS followed in the Texas Children’s Hospital (TCH) PWS clinic was obtained by an IRB approved chart review and parental report. Prenatal ultrasound findings and perinatal findings were abstracted from published reports.

Results: A total of 703 PWS cases were included (102 cases from TCH and 601 cases from published reports). The most commonly reported finding was maternal perception of decreased fetal activity (60-92% of cases). Other reported findings included fetal growth restriction/small for gestational age (18-65%), polyhydramnios (23-46%), and malpresentation (21-64%). Abnormal positioning of the limbs was reported in a small number of cases. 21-81% were delivered by Cesarean section. A combination of findings was reported in 24-34% of cases in one study.

Conclusions: A small number of third trimester fetal findings are associated with PWS and may constitute a “fetal phenotype” for the disorder. However, there is a wide variation in the proportion of PWS cases exhibiting the features in different cohorts and the most commonly reported finding, maternal perception of decreased fetal movement, is subjective and nonspecific. Further study is warranted to determine the utility of prenatal findings in the diagnosis of PWS.

IV-6. “Challenges in medical management of obesity hypoventilation in Prader-Willi syndrome”

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Introduction: Despite an extensive literature available on the syndrome, practical management of patients with Prader-Willi is poorly understood by well-trained clinicians who are generally encountering their first case. The author will delineate the most common and dangerous errors encountered in a consultation practice.

Methods: International clinical experience and consultation on cases of obesity hypoventilation in children and adults, eliciting recurring patterns of mismanagement.

Results: Treating physicians routinely fail to recognize the unique signs and stages of impending cardiopulmonary deterioration caused by obesity hypoventilation PWS: 1) nocturnal hypoxia; 2) non-pitting fluid retention; 3) daytime hypoxemia and dyspnea on exertion; 4) respiratory failure with or without *cor pulmonale*. Non-pitting edema responds to exercise and not diuretics.

Oxygen by nasal canula delivered at greater than 1 liter/minute without ventilatory support will suppress respiratory drive due to CO₂ insensitivity in PWS while body positioning can improve ventilation. Medications for agitation may add to sedation and narcosis. Exercise is lifesaving and precipitates a brisk diuresis but may be hampered by hospital culture and mismanagement of disruptive behaviors. Uncertainty about food (lack of psychological Food Security) precipitates intense behavioral disruptions and interferes with care. The difficulty of communicating the basic elements of Food Security to multiple hospital staff members necessitates that an informed family member or professional caregiver be with the patient at all times which also reduces the nearly universal anxiety and disruptive behavior seen in PWS patients during hospitalization. OT and PT consultations can play a critical role even in the ICU as nursing staff are not accustomed to getting ICU patients out of bed and moving.

Conclusions: Obesity hypoventilation is a serious medical condition which is life threatening but when recognized and treated appropriately can be reversed at all stages. Unfortunately, it remains the case that people with PWS die because obesity hypoventilation is considered the inevitable end stage of the syndrome. The lessons of clinical experience are difficult to communicate and transmit but in the case of rare disorders, such as PWS, are lifesaving because inexperienced clinicians are the rule, not the exception. The interface of medical and behavioral knowledge of PWS is especially important since after early childhood behavioral problems interfere with good medical care in a majority of cases of hospitalization.

V. General Medical Issues including Orthopaedics

V-1. Invited Talk: “The Orthopaedics of Prader-Willi Syndrome”

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Some of the important hallmarks of Prader-Willi syndrome are related to musculoskeletal issues, such as developmental delay due to their hypotonia, flat footedness, and scoliosis. We will discuss how this problems present, and what different options are for treating them from the perspective of a pediatric orthopaedic surgeon with a large patient population of children with PWS. Topics will include strategies for addressing developmental delay, for gaining muscle and bone strength, and monitoring and treating disorders of the hips in children with PWS. Extended discussion will focus on spine deformities, including bracing, spinal casting, expandable spinal implants and spinal fusion. Anaesthetic and post-operative recovery concerns for children with PWS undergoing surgery will be covered.

V-2. “Role of Body Cast Application for Scoliosis Associated with Prader-Willi Syndrome”

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Introduction: Approximately 40% of children with Prader-Willi syndrome (PWS) develop scoliosis, of which half develop their curves before 4 years of age, likely hypotonia related. Fifteen percent of all children with PWS will require surgical intervention. The complication rate for spine surgery in children with PWS is as high as 56%. This retrospective study evaluates the effectiveness of serial spinal casting to either correct a curve, or at least delay the necessity for expandable implant surgery, for infants and young children with PWS.

Methods: Since 2008, 32 patients with PWS had undergone spinal casting for scoliosis, of which 23 had a minimum of 2 years follow up after initial cast application. Criteria for casting included curves greater than 25°, or documented progression up to 25°, in children under 5 years of age. Radiographs were evaluated for Cobb angles and curve direction, rib-vertebral angle differences (RVAD), space available for lung (SAL), and Moe-Nash rotation for the initial pre-casting radiograph, and the last out of cast radiograph. Traction-release and in-cast radiograph were evaluated as well. Casts changes occurred every 2 to 4 months, dependent on the child's age. Curves were “cured” if their out-of-cast upright radiographs measured less than 15°, or less than 25° prior to three consecutive castings. Curves not “cured” would be controlled by casting or bracing until they were a suitable age for expandable spine implant surgery.

Results: The average age at initial cast application was 32 months (14 -64 months), an average of 8 casts (range 3-18) were applied, and the average follow up was 38 months. The pre casting Cobb angle of 58° (range 27-106°) was reduced to 37° (range 16-109°) at the latest followup. Curves were cured in 7 patients (6 uniparental disomy (UPD) and one deletion). Their average pre-casting curve was 42° (range 29° - 80°) which decreased to an average of 15° over 6 casts (3 - 8) spanning 17 months. At an average of 30 months since cast cessation, curves only increased to 18°. Three patients with large initial curves (54° - 109°) had placement of expandable spine implants an average of 51 months after initial cast, all three had deletions. Thirteen patients (5 UPD, 7 deletions, and one methylation defect) are either still undergoing casting or have been transitioned to bracing. Initial curves of 43° or less had an odds ratio of 37.5 for curve cure (P=0.0064).

Conclusions: Mehta style spinal casting is an important modality to treat infantile scoliosis in children with PWS. In general, curves less than 50° at cast initiation could be expected to reduce enough to allow graduation to a brace and subsequent weaning from brace. Curves larger than 50° could be controlled so as to postpone the need for surgery 3.5 - 5 years. This is a preliminary report, with a small sample size, due to the rarity of the PWS diagnosis. But it does appear that patients who start casting with a curve <50°, even at or slightly older than 3 years of age, have a favorable chance of a curve cure. It is encouraging that those with a cured curve continued to maintain a small curve over the brief followup period. There is a considerable concern, though, that once they reach early adolescents, the second peak incidence of scoliosis in PWS, that their curves may progress.

V-3. “High prevalence of scoliosis in a large cohort of patients with Prader-Willi syndrome”

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Introduction: Data about the prevalence of scoliosis in Prader-Willi syndrome (PWS) are not unequivocal, ranging from 15% to 86%. Furthermore, the role of growth hormone therapy (GHT) in the onset and progression of scoliosis remains controversial. In our study we investigated the prevalence and severity of scoliosis in a large group of patients with PWS, with and without GH treatment, evaluating the effects of age, gender, body mass index (BMI) and genotype.

Methods: A cross-sectional study was performed in 180 patients with genetically confirmed PWS (99 deletion, 78 UPD, 3 unknown), 96 females and 84 males, aged 17.6±12 yrs (mean±SD) (range: 1.3-49.7, median: 15.5 yrs), BMI: 29.0±11.2 [99 subjects (55%) with BMI >2 SDS were considered obese]. One hundred forty-eight subjects underwent GHT (previously or currently), while 32 patients have never been treated.

Apart from anthropometric data, we performed an x-ray of the vertebral column. Assessment of scoliosis, including Cobb Angles (CA) measurements, was performed by the same senior spine surgeon. Scoliosis was defined as a CA of >10°. Moreover, scoliosis was classified using the Scoliosis Research Society classification (2006), in mild (CA 10-20°), moderate (CA 20-40°) and severe (CA >40°).

Results: One hundred forty-eight subjects (82.2%), 80 females (54%), were affected by scoliosis (mild: n.51; moderate: n. 47; severe: n. 50), predominantly with thoracolumbar curve, rarely with a double curve. Mean age at diagnosis of scoliosis was 7.1±6.3 yrs (range 0.6-30.4 yrs).

A corset was prescribed to 77 subjects at the age of 7.6±3.9 yrs (0.7-15.2 yrs) and was worn for 4.8±3.3 yrs. Twenty-six subjects (14,4%) with severe scoliosis and high risk of progression underwent surgery at a mean age of 12.8±4.7 yrs (range 4-27 yrs).

The mean age at starting of GHT was 4.7± 5.6 yrs (0.1-32 yrs). GHT was observed in a similar percentage in subjects with scoliosis (122/148 = 82.4%) and in patients without scoliosis (25/32 = 78.1%). No statistical correlation was found between scoliosis prevalence and genotype (deletion: 83.8%; UPD: 82%) as well as gender (females: 83.3%; males: 80.9%). Scoliosis was present in 86% of patients >18 yrs and in 79.2% of children and adolescents ($p<0,05$). Out of 99 subjects considered obese scoliosis was observed in 85% of the cases, while the prevalence in non-obese PWS was 79%.

Conclusion: In our large cohort of PWS, scoliosis affects most patients (148/180 = 82,2%), with a high prevalence of moderate-severe forms (68.2%). In the latter, 69,6% of subjects underwent conservative or surgical treatment. Apart from age, our data indicate that scoliosis is intrinsic to the syndrome, regardless of gender, BMI and GHT. Therefore, we suggest to perform a spinal x-ray regularly in all PWS subjects, starting from the first years of

life, especially when the clinical and spinal examination is difficult due to the underlying obesity.

V-4. “Comparative Comorbidity Burden Among Patients With Prader-Willi Syndrome: A Population-Level Cohort Study”

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Introduction/Background: Prader-Willi syndrome (PWS) is a rare, complex multi-system genetic disorder characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to a significant burden on patients and caregivers. The hyperphagia seen in people with PWS can result in significant obesity. The objective of this study was to assess rates of comorbidities associated with obesity, including type II diabetes (T2D), cardiovascular disease (CVD), and sleep apnea (SA) in a large US PWS cohort versus a non-PWS cohort.

Methods: T2D, CVD, and SA conditions for privately insured PWS and non-PWS patients age <65 years were identified via ICD diagnosis codes in deidentified medical claims provided by IQVIA™ Health Plan Claims Data (1/2006 – 11/2018). Patients were required to have ≥12 months of enrollment, and patient observations were segmented into 12-month patient years.

Results/Discussion: 5,060 PWS and 31,093 non-PWS patient years representing 1,461 and 9,656 unique patients were eligible for analysis with comorbidity prevalence results below:

Age Group	0-2		3-8		9-17		18-26		27-34		35-49		50-64	
	PWS	Non PWS	PWS	Non PWS	PWS	Non PWS	PWS	Non PWS	PWS	Non PWS	PWS	Non PWS	PWS	Non PWS
Patient -years	457	1170	1187	2624	1623	4389	845	3809	338	3370	327	7748	283	7983
T2D	*	*	*	*	8%	*	19%	1%	27%	2%	27%	5%	27%	13%
CVD	25%	1%	11%	1%	15%	1%	29%	4%	44%	11%	60%	27%	78%	53%
SA	37%	*	22%	0%	17%	0%	18%	0%	18%	1%	15%	3%	16%	4%

*To be compliant with HIPAA, figures representing patient counts <11 are not reported

The largest disparities between PWS and non-PWS T2D prevalence were observed in the 9-17 and 18-26 age groups. Manifestations of CVD in PWS patients ages 0-2 include higher rates of congenital CVD, even after excluding secundum atrial septal and patent ductus arteriosus. The proportion of PWS patients with SA who received continuous positive airway pressure or oxygen monitoring ranged from 38% to 71%.

Conclusions: Across all age groups, compared to non-PWS subjects, individuals with PWS experience markedly higher rates of CVD, T2D, and SA. The increased rate of CVD in the earliest age groups is consistent with previously observed increases in congenital heart

defects with PWS. The frequency and early age of onset of hypertension, hyperlipidemia, T2D and SA emphasize the need for even more aggressive management of underlying drivers such as hyperphagia and the resulting obesity and metabolic dysfunction.

Funding source: Millendo Therapeutics provided funding support for this study.

V-5. “US prevalence & mortality of Prader-Willi syndrome: A population-based study of medical claims”

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Introduction: Prader-Willi syndrome (PWS) is a complex developmental genetic disorder associated with hypotonia, poor feeding in neonates, onset of hyperphagia in early childhood, and shorter overall life expectancy. Prior epidemiology studies of PWS have examined smaller populations, with only one study in a US population (Burd et al, 1990). The aim of this study was to provide a contemporary estimate of PWS prevalence and annual all-cause mortality in the US using a large administrative medical claims dataset.

Methods: PWS patients were identified between 2012-2014 via the presence of ≥2 claims with a diagnosis code for PWS on medical claims provided by IQVIA™ Health Plan Claims Data and CMS Medicare claims. PWS prevalence and mortality rates were calculated for 2014, and 2018 US census data was used to project rates for the total US population. The presence of select diagnoses and procedures suggestive of a life-threatening event (e.g., mechanical ventilation) with a patient’s prompt disenrollment defined as death in the IQVIA data; vital status is indicated in Medicare data.

Results: Overall US diagnosed PWS prevalence was 2.7 per 100k persons (or 1 per 37,037), a prevalence of 8,870 patients in the US in 2018. Diagnosed PWS prevalence increased from 3.9 to 5.2 per 100k between the 0-2 and 3-8 age groups before decreasing in subsequent older age groups. The median age of PWS patients was 21 years. Annual age-adjusted all-cause mortality was 2.7%. Mortality was highest among diagnosed PWS patients ages 0-2 years and lowest among those ages 9-17 years (5.4 and 1.4% respectively), with annual mortality increasing in each subsequent older age group. The observed median age of death was 23 years (IQR 6-36).

Diagnosed PWS prevalence and mortality in 2018							
Age group (years)	0-2	3-8	9-17	18-26	27-49	≥50	Overall
PWS per 100k	3.9	5.2	4.5	4.2	2.5	1.1	2.7
Unique PWS cases	459	1,257	1,690	1,673	2,465	1,325	8,870
All-cause mortality	5.4%	3.0%	1.4%	2.1%	2.4%	4.5%	2.7%

Discussion: The diagnosed PWS prevalence of 1 per 37,037 persons estimated for the 2018 US population is comparable to the only other reported US prevalence estimate (ref?). As the current study describes diagnosed patients, it likely represents a lower bound of true PWS prevalence. Annual PWS mortality is ≥3 times higher than the overall US population (2.7 vs 0.8%). This rate appears unchanged from mortality estimates reported for PWS populations in the last several decades despite significant advances in genetic testing and the availability of growth hormone therapies in the US. Aggressive management of serious comorbid conditions, especially in younger PWS patients, should be a clinical priority.

Funding source: Millendo Therapeutics, Inc. provided funding support for this study.

VI. Clinical Trials for Hyperphagia and Behaviour

VI-1. Invited Talk: “An Overview of Clinical Trials: Drug development process in Prader-Willi syndrome: Challenges and Opportunities”

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Clinical trials have been fundamental in fostering the development of novel treatments in medicine and for understanding disease mechanisms. Since 2012, the number of clinical trials testing new drugs for PWS has been multiplied by four. Drugs with different mechanisms of action are being tested opening avenues for better understanding the biology underlying PWS. While this raises the hope that new treatments will be available in the near future, there are a number of challenges and barriers at each stage of the therapeutic development process that could impede successful clinical trials outcomes and access to meaningful therapies for individuals with PWS. An overview of the R&D stages and process for bringing a therapeutic candidate to clinical trial and access to patients as well as efforts undertaken by the PWS community to address challenges will be discussed in the context of the specificities of rare diseases and PWS.

VI-2. “Tesomet - a new treatment opportunity in Prader Willi Syndrome. Results from Phase 2a exploratory studies in adult and adolescent patients”

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Introduction: Prader-Willi syndrome (PWS) is a debilitating, multi-faceted genetic disorder with no effective treatment. One of the hallmarks of this syndrome is insatiable appetite and constant drive to seek food. Tesomet, a combination of tesofensine (a noradrenaline, dopamine and serotonin reuptake inhibitor) and metoprolol (a β 1-adrenergic blocker) has demonstrated a significant effect on satiety, appetite and food craving in several patient populations and is now also evaluated in PWS patients as a potential therapy for hyperphagia and overweight in this syndrome.

Methods and results: The Phase 2a exploratory study was conducted at two centers and in two parts: *Part 1*, a 12 week double-blind placebo-controlled study (randomized 2:1 with 0.5/50 mg of tesofensine/metoprolol in active arm), in nine adult patients; results were reported in 2018 and showed strong reduction in hyperphagia score (HQ-CT scale). Active arm: Reduction in hyperphagia score from 10 at baseline to a mean score of 0 at 12 weeks (mean score of 1 at 8 weeks). The mean weight loss was 6.75% in the active and 0.75% in the placebo arm. Four patients completed the study; noteworthy adverse events were exacerbation of pre-existing behavioral and psychiatric issues. No SAEs were reported. *Part 2* of the study enrolled adolescent patients aged 12-18 and was a double-blind, randomized (2:1), placebo-controlled (0.125/25 mg tesofensine/metoprolol and matching placebos), 12-week study, followed by a 12-week open-label extension (OLE1; all patients on Tesomet 0.125/25 mg) and then another 12-week open-label extension (OLE2; patients on Tesomet 0.25/25 mg) if deemed eligible by the investigator and consented to participate. All patients were returning to the sites monthly. Primary endpoint was body weight, secondary endpoints hyperphagia score (HQ-CT), safety (AEs vital signs, ECG, labs), waist circumference, metabolic endpoints and PK. Nine patients were enrolled in the placebo-controlled part; 8 patients agreed to continue into OLE1 and 4 patients into OLE2. The treatment was in general well tolerated; the most frequently reported AEs were headache, insomnia, dizziness, restlessness, palpitations, mood disorders. One non-related SAE was reported. There was no significant effect on the vital signs or laboratory parameters. Part 2 is still ongoing the full data will be presented at the meeting.

Conclusions: Based on data from this Phase 2a exploratory study Tesomet appears to have the potential to provide strong efficacy on hyperphagia and weight with a favorable risk/benefit profile.

VI-3. “Trial-in-Progress: ZEPHYR, a Pivotal Phase 2b/3 Randomized, Placebo-Controlled Study of Livoletide, a Novel Unacylated Ghrelin Analogue, for the Treatment of Hyperphagia and Food-Related Behaviors in Patients With Prader-Willi Syndrome”

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Background: Prader-Willi syndrome (PWS) is a rare, complex neuro-developmental genetic disorder characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to a significant burden on patients and caregivers. There is no approved treatment for hyperphagia in PWS. People with PWS have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG). Livoletide (AZP-531) is a first-in-class UAG analogue that was previously shown in a Phase 2 randomized, double-blind, placebo-controlled study of 47 PWS patients to significantly improve hyperphagia, food-related behaviors, and metabolic parameters, and to be well-tolerated. [Allas S et al (2018) PLoS ONE 13(1): e0190849]

Objective: ZEPHYR (EudraCT 2018-003062-13; NCT03790865) is a pivotal Phase 2b/3 study that is designed to evaluate the long-term safety and efficacy of livoletide in patients with PWS.

Methods: The ZEPHYR study is currently being conducted in North America and Europe. In its Phase 2b portion, approximately 150 patients with PWS will be randomized to receive livoletide ~60 µg/kg, livoletide ~120 µg/kg, or placebo, once daily by subcutaneous injection for a 3-month core period. Patients will then enter a 9-month extension period where all subjects receive livoletide. The Phase 3 portion will be initiated following results of the Phase 2b core period with patients randomized to livoletide at a single dose based on Phase 2b core data or to placebo. After 6 months of treatment in the Phase 3 core period, patients will enter the 6-month Phase 3 extension period where all subjects receive livoletide.

Main entry criteria for ZEPHYR include genetic diagnosis of PWS, age 8-65 years, single primary caregiver available for the duration of the study, and body mass index (BMI) ≤65 kg/m² for adult patients. Patients with type 2 diabetes with HbA1c ≤10% may be enrolled. Use of human growth hormone will be allowed if dosage is stable.

The primary outcome measure is the Hyperphagia Questionnaire-Clinical Trials (HQ-CT) score. The HQ-CT has been validated and is considered by regulatory authorities to be a valid primary endpoint. Secondary outcome measures include metabolic and body composition parameters such as fat mass as assessed by DEXA, BMI, and body weight in overweight/obese patients.

Results: The study is ongoing. Enrollment began in early 2019 and updates will be reported.

Conclusion: ZEPHYR is a pivotal study that will provide data on the long-term safety and efficacy of the novel UAG analogue livoletide on the treatment of hyperphagia and food-related behaviors in patients with PWS.

Funding source: Millendo Therapeutics provided funding support for this study.

VI-4. “Effect of topiramate on eating behaviours in Prader-Willi syndrome”

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Introduction: Prader-Willi Syndrome (PWS) is a rare genetic syndrome leading to severe behavioural disorders and mild cognitive impairment. The objective of this double-blind randomized placebo-controlled trial was to study the efficacy and tolerance of topiramate on behavioural disorders in patients with PWS.

Methods: Participants (aged 12 to 45 years) had genetically confirmed PWS and severe irritability/impulsivity, eating disorders and/or obesity, and skin picking. Thirty-two participants received a placebo (PBO), and 30 participants received topiramate (TOP) (50 to 200 mg/day) for 8 weeks. The primary outcome was the rate of responders using the Clinical Global Impression-Improvement (CGI-I) scale. The secondary outcome measures included the Aberrant Behaviour Checklist, the Dykens Hyperphagia Questionnaire (DHK), the Self-Injurious Behavior Scale (SIBS) and the body mass index (BMI).

Results: We found no significant difference in the primary outcome (the CGI-I): 9 (30%) patients were very much or much improved in the TOP group compared to 7 (22.6%) patients in the PBO group. However, the DHK behaviour and severity scores improved significantly more over time in patients treated with topiramate versus those receiving a placebo, with a significant dose-effect relationship. DHK scores were also significantly associated with genetic subtypes and hospitalization status. The effects of topiramate on eating behaviours remained significant after adjusting for genetic subtype and hospitalization.

Conclusions: Topiramate had therefore a significant effect on eating disorders, with a dose-effect relationship. Given the burden of eating disorders in PWS, we believe that topiramate may become the first psychotropic option within the global care of obesity in individuals with PWS.

VII. Mental Health, Behaviour & Cognition #1

VII-1. Invited Talk: "Mental Health and Behavior in PWS"

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The behavioral and mental health phenotype of PWS evolves across development, although the mechanisms for this progression are not understood. There are several processes that occur during typical brain development that may help to explain this progression, although the precise manner in which these mechanisms interact with the developing brain in PWS is less well understood. These developmental mechanisms include:

1. Neurochemicals in the brain that take on different properties or effects across development, e.g., "the GABA brake" during the transition from the neonatal period to infancy;
2. Genomic imprinting mechanisms that may regulate how genes turn on and off across development;
3. The process of myelination as the brain matures that allows areas of functional specialization, primarily in the cortex, to come "on line" and assert influence over previously connected "hard wired" subcortical regions;
4. Epigenetic mechanisms related to stress and environment that alter gene expression across development; and
5. The phenomenon of "critical periods."

There are several descriptive models derived from the phenomenology of PWS that have been developed to identify the emergence and progression of behavior in PWS, such as the appearance and course of temper tantrums and the nutritional stages of hyperphagia. Also, there are hypothetical constructs for understanding the behavioral phenotype: the reward hypothesis, the satiety and feedback deficit hypotheses; the autonomic dysregulation hypothesis, and the emotional salience hypothesis.

In this talk, an overview of the progression of behavior and mental health symptoms across development in PWS will be described with specific attention to phenomenology, models of brain development, evidence from brain imaging, and the current understanding of contributions from genetics, stress, and aging. Implications for prevention and timely management of symptoms will be discussed.

VII-2. “Cognitive functioning in children with Prader-Willi syndrome during 8 years of growth hormone treatment”

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Introduction: Children with Prader-Willi syndrome (PWS) generally have mild to moderate cognitive impairment with an IQ between 60 and 70. Growth hormone (GH) treatment is a registered treatment for children with PWS and has been associated with cognitive benefits, attributed to the effects of GH and insulin-like growth factor on brain growth and development. Short-term data suggest positive effects of GH treatment on cognitive functioning in children with PWS.

Methods: In this prospective cohort study we longitudinally investigated the effects of 8 years of GH on cognitive functioning in 43 children with PWS. We also investigated whether starting GH early resulted in higher cognitive functioning after 8 years of GH. All children were treated with GH 1 mg/m²/day (≈0.035 mg/kg/day) and followed at the Dutch PWS Reference Center. Cognitive functioning was assessed by the Wechsler Intelligence Scale for Children (WISC). Vocabulary, Similarities and Block Design subtests were used and expressed as standard deviation scores (SDS). Total IQ (TIQ) was estimated.

Results: Forty-three children with PWS (29 girls) started GH at a median (IQR) age of 8.1 (6.6; 11.5) years. Estimated mean (95% confidence interval, CI) Block Design SDS changed from -2.2 (-2.6; -1.8) at baseline to -1.8 (-2.2; -1.4) after 8 years of GH (p=0.18), showing a modest trend towards an improvement of visuospatial skills in children with PWS. Similarities SDS changed from -1.5 (-2.1; -0.9) to -1.3 (-1.9; -0.7, p=0.66) and Vocabulary SDS remained similar, being -1.9 (-2.3; -1.4) at baseline and -1.9 (-2.4; -1.5) after 8 years (p=0.85), demonstrating that children with PWS develop abstract verbal reasoning and vocabulary at the same pace as healthy references. Mean estimated (95% CI) TIQ changed from 66 (60; 72) to 69 (63; 75, p=0.57).

We compared WISC results after 8 years of GH of the 43 longitudinally studied children who started GH during childhood to a separate group of 22 children from our Dutch PWS Cohort who started GH at a median (IQR) age of 1.4 (1.0; 1.8) years. We could not evaluate the longitudinal effects of 8 years of GH in the latter group, because WISC is not suitable for children younger than 6 years of age. After 8 years of GH, the 22 children who started GH during infancy scored significantly higher on the Vocabulary subtest (p<0.01), resulting in a higher estimated TIQ (p=0.04). Scores on the Block Design and Similarities subtests were similar between the two groups (p=0.48 and p=0.16, resp.).

Conclusions: Our results demonstrate that cognitive development during 8 years of GH in children with PWS remains similar and progresses at the same pace as healthy peers. Furthermore, early start of GH, in a critical period of neurodevelopment, might be beneficial for long-term cognitive functioning.

VII-3. “A Genotype-Phenotype Analysis of the Effects of Growth Hormone Treatment on Psychiatric Behavior in Prader-Willi Syndrome”

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Introduction: This study aims to describe the frequencies of nine psychiatric behaviors found in PWS (depressed mood, anxiety, compulsions, skin picking, nail picking, compulsive counting, compulsive ordering, playing with strings, visual hallucinations, and delusions) as well as investigate their association with growth hormone treatment (GHT) for the most common molecular types: deletions (DEL) and uniparental disomy (UPD).

Methods: Retrospective guardian reported data were compiled from the Rare Disease Clinical Research Network’s Natural History PWS and Morbid Obesity Clinical Protocol. Inclusion criteria included a confirmed diagnosis of PWS, 14+ years of age by last visit, and known GHT status. Out of a cohort of 355 individuals, 172 fulfilled criteria. Statistical analyses were performed using SPSS Statistics Software. Associations between use of GH and psychiatric phenotype were explored using Pearson Chi-Square tests and univariate and multivariate logistic regression analyses were employed to control for other confounding exposures. An interaction between GHT and genetic type was added to the univariate model.

Results: Among our cohort of 172 participants with PWS, 62.2% had DEL, 33.1% had UPD, and 4.7% had an imprinting center defect (ICD). Of those with DEL or UPD (n=164), 70.7% were on GH (72.9% and 66.7% respectively, $p=0.404$). A significant difference in skin picking frequency for those with DEL vs. UPD was identified (81.9% vs 63.2%, $p=0.009$). There was also a significant difference in anxiety frequency for individuals with DEL on GH vs. no GH cohorts (83.1% vs 16.9%, $p=0.007$). After adjusting for covariates, individuals with UPD had a higher presence of anxiety than those with DEL (OR=7.567, 95% CI: 1.781-32.146, $p=0.006$). Relative to those with DEL who did not use GH, those with UPD who used GH had a 3.25 fold increased presence of anxiety, whereas those with DEL who used GH had a 2.73 increased risk in anxiety. The other differences were not significant.

Conclusions: These results suggest that genotypic-phenotypic differences in psychiatric behaviors exist where skin picking is more frequent in those with DEL and GH was shown to have a higher association with increased anxiety for those with UPD vs. those with DEL. The data, however, are subject to a number of limitations. Psychiatric phenotypes are based only on guardian report. Furthermore, associations may reflect confounding from unmeasured covariates or chance due to multiple outcomes. As these results were unexpected in this preliminary study, more rigorous testing of a limited number of hypotheses as well as studies with more consistency in growth hormone treatment, onset, and duration are required before any conclusions can be reached and validated.

VII-4. “Gray matter microstructural alteration of the brain in individuals with Prader-Willi syndrome: a 7T MRI study”

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Introduction: There is much research into common behavioral characteristics and developmental trajectories in individuals with Prader-Willi syndrome (PWS). This has contributed to our better understanding of behavior and mental health issues in PWS. Existing data suggest neurological underpinnings of both structural and functional alterations of the brain during its development in this population. We previously reported on white matter (WM) microstructural alterations using diffusion tensor magnetic resonance (MR) imaging. However, given the specific functional alterations relevant to the clinical behavioral patterns, structural connectivity should be simultaneously analyzed across gray matter (GM) and WM microstructures using an advanced diffusion imaging based on an ultra-high-field MR system. We hypothesized that developmental abnormalities of GM and WM microstructures exist in the brain of individuals with PWS.

Methods: Eleven individuals with PWS who manifested behavioral and developmental problems (age range: 15–42 years; male 8, female 3; Del 10, UPD 1), as well as age- and gender-matched typically developing controls participated in the study using a 7Tesla MR system. Diffusion characteristics—as indexed by neurite dispersion index (NDI), orientation dispersion index (ODI) using NODDI based on non-gaussian distribution assumption, and fractional anisotropy (FA) were assessed for cerebral cortical and subcortical structures. A whole brain analysis was performed complementary to a focused region-of-interest (ROI) correlation analysis with clinical behavioral pictures based on anatomically guided detection of cluster areas.

Results: We observed significantly reduced FAs in previously reported brain areas in individuals with PWS. Moreover, scattered increases in NDI and ODI were detected in multiple brain regions over the frontoparietal, temporal, and subcortical areas in the whole brain map. The ROI analysis subsequently identified significant correlations between maladaptive behavior scores and ODI ($p < 0.05$, FWE corrected) in the bilateral frontal cortical areas in individuals with PWS compared to controls.

Conclusions: The observed altered diffusion characteristics indicate attendant developmental abnormalities within both GM and WM structures. These abnormalities were associated with observed clinical and behavioral patterns in individuals with PWS. The 7T study provides objective evidence regarding the effects of PWS on altered microstructural GM connectivity.

VII-5. “Bilingualism and Executive Control: the PWS population on the spotlight and... doing well”

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Introduction: The executive Control (EC) capacity, which allows us to “successfully” carry out our daily life tasks, has been extensively scrutinized in Typically Developing (TD) individuals with the aim of understanding the relation between bilingualism and cognition. Inhibition, the capacity to focus on a specific task neutralizing non-relevant information, has been one of the processes that has attracted most attention. Given that bilinguals are used to have two languages activated at the same time and, for the most part, are constantly dealing and alternating between them, many studies have argued that this gives them an advantage over monolinguals to ignore non-relevant information, which, in turn, seems to result in better inhibition abilities (Valian 2015). However this “solid” bilingual “advantage” has lately been put in doubt arguing a possible publication bias towards positive outcomes of bilingualism over a neutral or negative effect of it (de Bruin et al. 2015). Thus, the main aim of this research was to study the inhibition capacity of bilinguals and monolinguals with a developmental disability with intellectual disability (ID), as is the case of PWS, to enlighten how bilingualism shapes their EC, since bilingualism is normally discouraged for this population without scientific evidence of its detrimental effect.

Method: 8 Spanish monolinguals and 7 Catalan-Spanish bilinguals with PWS completed two tasks intended to measure their EC capacity: a Flanker task (non-verbal) and a Stroop task (verbal). Both tasks were programmed in E-prime 2.0 and presented on a laptop computer. In the Flanker task five chevron sequences were presented and participants had to determine the direction of the central chevron (right or left) as quick as possible. Three stimuli conditions (32 items per condition) were included: (1) congruent (central chevron pointing to the same direction as the others chevrons), (2) incongruent (central chevron pointing to the opposite direction of the other chevrons) and, (3) control (only one chevron between four dashes -two in each side). In the Stroop task different color-colored words were presented and participants had to tell the font color in which the words were written. Three stimuli conditions (36 items per condition) were included: (1) congruent (color word and color font coincide), (2) incongruent (color word and color font do not coincide) and, (3) control (non-color word written in red, yellow or blue). For both tasks each trial consisted of an “Are you ready?” screen (response required) followed by a centered fixation cross presented during 500ms, followed by the target, which remained on screen until a response was provided. Participants responded using an USB numpad. Both reaction-time (RT) data and accuracy rates (ARs) were analyzed.

Results: Preliminary results do not reveal significant differences between groups neither for RTs nor for ARs in any of the two tasks. However, there was a main effect of condition in RT data in both tasks. In the case of the Flanker task, it revealed the following scale: Incongruent > Congruent > Control, and in the case of the Stroop task showed that incongruent items exhibited higher RTs than congruent or control items (Stroop effect). These findings are in line with previous findings from TD individuals.

Conclusions: These results show that bilinguals and monolinguals with PWS do not differ with respect to EC ability, which is in line with the results of the limited previous research focused on bilingualism and IDs (Kay-Raining Bird et al. 2016), and challenges the extended

practice to discourage these individuals to learn a second language (or a Heritage language) under the unfounded assumption that this could have a negative effect on their cognitive development.

VIII. Mental Health, Behaviour & Cognition #2

VIII-1. “Flexible scheduling to prevent the development of disabling resistance to change: acceptability and feasibility of a digital intervention co-produced with stakeholders”

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Introduction: Negative emotional and behavioural responses to altered routines or expectations – *resistance to change* - is common in individuals with PWS. It is a major trigger of behaviour problems [2-3], which may be disabling in their impact on the individual and their family. Growing evidence suggests that flexibility early-in-life may reduce later resistance by enhancing the development of task-switching, a cognitive process that appears to contribute to the effective management of change. This study aims to develop an intervention, which systematically increases variability in children’s environments in a way that provides necessary structure for managing current behaviour challenges, alongside necessary flexibility for appropriate cognitive training.

Methods: An iterative collaborative design process was conducted with professionals (n=12) and families of children between 5-12 years with a diagnosis of PWS (n=15) or another neurodevelopmental disorder linked to resistance to change (n=21). Design specifications that would allow the intervention to meet families’ needs were identified via individual interviews with caregivers (n=36). These criteria were used to create a paper prototype of the intervention, which was refined via focus groups with caregivers (n=13). A functional online prototype was then created, and tested at home by families in three stages (1-2 weeks) with iterative improvements being integrated throughout (n=12). Semi-structured individual interviews and questionnaires assessed acceptability and feasibility for all caregivers involved in testing. Focus groups with parents and children from three families further informed on these issues.

Results: All participants rated ‘agreement’ or ‘strong agreement’ on the potential benefits for their child, that it was an acceptable way to manage a difficulties with flexibility, and it would likely improve behaviours around change. Participants reported that the ‘game-like’ experience was exciting, it helped children manage changes they historically have found difficult, and that motivation was maintained.

Conclusions: Participants had an overall positive reaction to the intervention with reports that the integrated strategies supported parental confidence and management of current challenging behaviours. However, to increase motivation to engage long-term, children should have the capacity to personalise the graphics, and attainment of short-term goals should be noticeable for parents. With such refinements, the intervention has the capacity to provide families with remote-access to evidence-based behaviour principles, which can have an immediate positive impact on the experience of children and their families.

VIII-2. “A randomised control trial to evaluate the impact of engagement with a task switching training computer game on people with Prader-Willi syndrome”

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Introduction: Resistance to change in expectations is part of the behavioural phenotype of Prader-Willi syndrome (PWS) and unexpected changes are one of the most common triggers of temper outbursts. Our own and others' previous research has demonstrated specific deficits in the executive process task switching in people with PWS. Importantly, work in PWS and other populations suggests a link between task switching deficits and resistance to change. We developed a computer-game to improve task-switching in children with PWS. An early prototype, appeared capable of improving task-switching skill in children with PWS. Here, we aimed to fully develop the prototype in an iterative collaborative process and evaluate how far engagement with the game could improve task switching skill and resistance to change behaviours.

Methods: “The Three Crowns” game was developed from our early prototype based on PWS families' experiences of engaging with the prototype, and over the course of an iterative process including three design workshops with young autistic people (autism is linked to resistance to change and including autistic people limited the exposure of people with PWS to the game before commencement of the evaluation, as such prior exposure could limit engagement).

In a double-blind placebo controlled design, randomised minimisation was used to allocate participants with PWS (n=30) to matched active training or placebo groups (same game, task-switching demands removed). Assessments were completed immediately prior to and following a 5-week game engagement period. Assessments included 4 direct tests of task switching (computer based) and parent report questionnaires on resistance to change, associated challenging behavioural responses, and behavioural indices of task-switching deficits. Parents also completed an online behaviour diary during a baseline and the engagement period. Following the engagement period, families were invited to take part in a 5-week follow up period, when all participants received the active version of the game, followed by an unstructured parent report interview on experience during the trial.

Results: Results varied across outcomes, and across individuals who engaged with the game over different durations. The efficacy and feasibility of the training will be discussed.

Conclusions: There may be some potential for computer games to be used to improve task switching and associated behavioural problems in some people with PWS. However, timing, dosage and individual cognitive and behavioural profiles may affect outcomes and more research is needed to allow such an approach to be appropriately targeted.

VIII-3. “Specific features in the expression of emotions in children with Prader-Willi syndrome : What are the consequences for emotion abilities and social adjustment?”

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Introduction: People with Prader Willi Syndrome (PWS) have great difficulties of social adaptation that could be explained by disturbances of emotional competencies (i.e. ability to use emotions daily). However, we currently have incomplete knowledge about the emotional functioning of people with PWS and even more about its development during childhood. In particular, the emotional expression abilities (facial, bodily) have never been investigated while they are at the foundation of the establishment of interpersonal relationships and thus of social adaptation. In addition, the motor and cognitive difficulties - characteristic of the PWS - could further impair these abilities. The objective of this study was, among other things, to explore precisely the expression abilities of children with PWS.

Method: Twenty-five French children with PWS aged 5 to 10 years were assessed for 1) their emotional facial reactions to a funny video-clip and 2) their ability to deliberately produce the facial and bodily expressions of joy, anger, fear and sadness. Their productions have been compared to those of two groups of children with typical development (TD); matched to PWS children, on the one hand, by chronological age, and, on the other hand, by developmental age.

Results: The results showed that children with PWS presented as many emotional facial reactions as TD children. However, many ambiguities have been noted in their facial expressions, making them particularly confusing. Precisely, we observe in expressions a lot of mixture of different emotional patterns (e.g., some parts of disgust or fear patterns in laughter expressions). In addition, it has been observed that the deliberate emotional productions of PWS children have been particularly minimalist and confused.

Conclusions: This study was able to highlight the existence of particularities in the expression of emotions in PWS children. These results shed new light on the emotional functioning in the PWS and consequently on the adaptive abilities of these people in the daily life.

VIII-4. “PRACOM 2 project: Study of the emotional aspects associated to behavioral and cognitive troubles in the Prader-Willi Syndrome”

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Introduction: Prader-Willi Syndrome (PWS) is a rare genetic pathology characterized by several behavioral and cognitive disorders (Whittington & Holland, 2017). Temper tantrum is one of the most frequent maladaptive behaviors in the PWS (Rice et al., 2018) associated with emotional lability (Woodcock et al., 2011) and widely described in the literature. However emotional features associated to this behavior and their relationships with cognitive and social aspects are less known. The project PRACOM 2 is part of a wider project called PRACOM (PRADER-Willi Communication) which aim is to identify emotional characteristics of adults with PWS that are associated to their behavioral disorders (especially anger behavior) which can be an obstacle for social integration and communication. In PRACOM 2 we focused as well on patient's cognitive abilities to process emotional information and on the repercussions for the well-being of parents.

Methods: For the project, we will include 30 patients with PWS, 30 adults without pathology (matched on age and sex) and 30 parents of patients (one of them). Three sessions of evaluations (questionnaires and cognitive tasks) of 1h30 are proposed to the two groups of participants and one remote session (questionnaires and interview) for the patient's parents. Questionnaires of emotional regulation, emotional lability, emotional reactivity, irritability and depression are used to characterize emotional features of adults with PWS. The evaluation of behavioral disorders (e.g., hyperphagia, temper tantrum) is also made through questionnaires. Moreover, the well-being of parents is evaluated by an interview about their needs and questionnaires about their quality of life and burden. Finally, to examine the cognitive abilities of people with PWS to process emotional information, we propose an emotional lexical decision task. In this task, participants have to decide if letters presented on a computer screen represent a word (e.g., *family*) or not (e.g., *faurt*). Words can reference joy, sadness, anger or neutral. If patients can process efficiently emotional information, recognition times could differ according to the emotional content of words compared to neutral ones.

Results: First results on 15 adults with the SPW (mean age = 32,33) and 25 adults without pathology (mean age = 32,16) have showed that people with PWS demonstrated a higher level of depression, irritability, emotional lability, emotional reactivity and difficulty to suppress their affect compared to people without the pathology. Moreover, emotional lability and irritability were the only factors associated to behavioral troubles. Furthermore, a high-level of emotional lability, depression and irritability of patients negatively impact the quality of life and burden of parents. Finally, results of the emotional lexical decision task showed that patients process emotional words efficiently. Overall, these first results suggest difficulties in PWS patients to control their affective state but good abilities for processing emotional information.

Conclusions: Benefits of the PRACOM 2 project concern the improvement of the knowledge related to the emotional functioning of adults with PWS and the factors regulating behavioral disorders. Among others, this will allow a better management of the syndrome by family and clinical staff.

Clinical and Scientific conference: Poster abstracts

I. Genetics, Epigenetics & Animal Models

Poster #1 Narrowing the critical deletion region of Prader-Willi syndrome: Extremely mild phenotype caused by an extremely small deletion of the Prader-Willi region

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Introduction: Prader-Willi syndrome (PWS; OMIM #176270) is a rare condition (1:25.000 births) affecting many organ systems. PWS is characterized by mild to severe mental retardation, extreme appetite (hyperphagia) and pituitary hormone deficiencies. Usually, PWS occurs due to the absence of expression of a cluster of paternally expressed genes located in the PWS region on chromosome 15q11.2-q13, either due to uniparental maternal disomy (mUPD, 30%), an imprinting center defect (ICD, <5%) or a paternal deletion (DEL, 70%). The deletion class is typically subdivided into Type 1 and Type 2 based on their proximal breakpoints. Despite PWS being a well-characterized genetic disorder, the role of the specific genes contributing to various phenotypic features are not well understood. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) is a technique that detects copy number changes and aberrant DNA methylation. We describe a patient with PWS who had an extremely mild phenotype, in whom we have applied MS-MLPA to elucidate the deletion subtype.

Methods: We collected genetic and phenotypic data of all 120 adults with PWS attending the outpatients clinic for adults with PWS. In one patient with an extremely mild phenotype, we performed methylation specific PCR which revealed a paternal deletion. In order to find an explanation for his extremely mild phenotype, we additionally carried out MLPA using kit ME028-B2 PWS/AS (MRC Holland) to delineate the deletion.

Results: Among 120 patients attending the outpatients clinic for adults with PWS, genetic analysis revealed ICD in 3%, mUPD in 27% and a deletion in 70%. One patient with a deletion had an extremely mild phenotype. Although he had had hypotonia and feeding difficulties at birth, at adult age he had normal IQ, almost no hyperphagia and he had even obtained his driving license. He had only mild autisticiform features and led a nearly normal social life. He did not have growth hormone deficiency or adrenal insufficiency. Whereas severe hypogonadism is present in almost all PWS adults, he had normal pubertal development. In order to find an explanation for his extremely mild phenotype, we carried out MLPA, which showed an abnormal pattern for 21 consequent probes located in SNRPN and UBE3A. For all other probes, a normal pattern was seen.

Conclusion: We report a PWS patient with a remarkably mild phenotype, caused by an atypical, unusually small deletion. The deletion only affected SNRPN and UBE3A and none of the other genes in the Prader-Willi region. Functional impact of this deletion will increase our knowledge of the pathophysiology of Prader-Willi syndrome

Poster #2 Homozygous *SNRPN* point mutation as a potential new cause of Prader-Willi (like) syndrome

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Introduction: Prader-Willi syndrome (PWS) is generally believed to be caused by loss of expression of an entire cluster of paternally expressed genes within the PWS region on chromosome 15, due to deletion, uniparental disomy or imprinting center defects. We describe a unique patient with the complete spectrum of PWS features, in whom these regular causes were excluded. Additional genetic testing revealed a homozygous point mutation in *SNRPN* (one of the genes located in the PWS region), which was located in a large homozygous region (the parents were first-degree relatives). *SNRPN* encodes snRNP polypeptide N (SmN), which is highly expressed in the brain and is involved in neurite outgrowth, neuron migration and distribution of dendritic spines in mice. However, the precise role of *SNRPN* in the development of the PWS phenotype still remains largely unknown. This patient is unique, because point mutations in a single gene have never been described before as the cause of PWS.

Methods: In the index patient, we performed methylation testing, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis, SNP array and obesity gene panel analysis, targeted analysis of 52 obesity-related genes using automated sequencing.

Results: In the 46-year-old female index patient, genetic diagnosis of PWS was initially rejected after regular genetic tests for PWS showed normal results. We performed additional obesity gene panel analysis, which identified a homozygous point mutation in *SNRPN*, located in a large homozygous region on chromosome 15.

Conclusion: Until now, it was generally accepted that Prader-Willi syndrome could only be caused by functional loss of an entire cluster of genes within the PWS region on chromosome 15q11.2-q13. The unique finding of a homozygous point mutation in a single gene of this region (*SNRPN*) in a patient with virtually all features of PWS, contributes to the unravelling of the pathophysiology, and the role of SmN in PWS.

Poster #3 Algorithm for the diagnosis of Prader-Willi syndrome in Cuba.

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Introduction: Prader Willi syndrome is a complex genetic disease caused by different genetic mechanisms that result in the physical or functional absence of a group of genes on chromosome 15. Clinical analysis can be complicated when it comes to Prader-Willi syndrome because to the existence of phenotypic traits that may be common to other genetic abnormalities.

Objective: Describe a working algorithm for the diagnosis of Prader Willi disease.

Result: 62 patients with clinical suspicion of Prader-Willi syndrome were analyzed. 31 individuals with the disease were detected, through studies of conventional karyotype, FISH and methylation analysis. 28 presented the deletion on the maternal chromosome 15 corroborated by FISH.

Conclusions: Through the correct clinical analysis of the patient, the use of the methylation test and the FISH technique, an accurate diagnosis of the disease is achieved in a number of cases despite the genetic heterogeneity that accompanies the clinical manifestations in these children.

Poster #4 Clinical and genetic characterization of a group of children with phenotype suggestive of Prader-Willi syndrome

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Introduction: Prader-Willi syndrome (PWS) is a genetic disorder characterized by hypotonia and feeding difficulties in infancy, followed by hyperphagia, hypogonadism, mental retardation, and short stature. Its clinical features tend to be confused with several other disorders and its diagnosis is not always as early as it could be.

Methods: A review of 15 clinical histories of children (7 males and 8 females) with features of Prader-Willi syndrome was performed in order to delineate the main phenotypic signs and genetic defect.

Results: Prenatal history of fetal inactivity and breech presentation was found in 66% of patients, while severe hypotonia and feeding problems in neonatal period were present in 100%. Poor sucking and weight gain in early infancy and hyperphagia after 6 months were found in all cases with the result of 6 patients (40%) with moderate obesity and 9 (60%) with a severe one. All patients had small hands and feet, typical facial features and neurodevelopmental delay, but only 4 females had hypogonadism while all males had it. Intellectual disability was described in all the eldest patients. The mean age at diagnosis was 2 years old ranging from 15 days to 18 years. Despite some problems with cytogenetic and molecular analysis of PWS that makes difficult the diagnosis, a *de novo* deletion of 15q11-q13 was found in 4 patients and methylation defects in another 4 suggesting maternal uniparental disomy. In one patient a balanced chromosomal translocation involving 15q11 was detected. The rest of the patients are still pendants of molecular confirmation.

Conclusions: Prader-Willi syndrome should be suspected in any infant with early severe hypotonia and feeding problems. Cytogenetic and molecular studies should be performed in these cases in order to confirm or deny the diagnosis.

Poster #5 Molecular Diagnosis of Prader-Willi Syndrome in Cuba

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Introduction: Prader-Willi Syndrome is a genetic disorder caused by the loss of function of genes in the 15q11.2–q13 region of the paternal chromosome. It is characterized, among other manifestations, by hypotonia, hypogonadism, hyperphagia, short stature and delay of neurodevelopment. DNA methylation analysis is a molecular technique that allows the study of this disease and thus the diagnosis of any of the main genetic mechanisms that cause it, such as, deletions, uniparental disomy and imprinting defects at chromosome 15. This study aims to perform the molecular diagnosis of Prader-Willi Syndrome through the methylation-sensitive polymerase chain reaction (MS-PCR).

Methods: Genomic DNA isolation of a total of 66 blood samples, mouth scraping or amniotic fluid by manual or automated extraction was performed. Subsequently, the extracted DNA was treated with sodium bisulfite through the EZ DNA Methylation kit for the next realization of the polymerase chain reaction using specific primers that allow specific amplification of maternal alleles and paternal of the SNRPN gene. The results were visualized under ultraviolet light in Agarose MS gel at 3% dyed with ethidium bromide.

Results: 100% of the samples were diagnosed, with 40 negative and 26 positive individuals, molecularly confirmed by conducting this study, which also enables the availability of a molecular diagnostic method in the country.

Conclusion: The MS-PCR technique is a fast, economical and highly sensitive method that enables molecular diagnosis of Prader-Willi Syndrome.

Poster #6 Chromosomal aberrations detected in patients with Prader Willi like phenotype

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Introduction: Prader Willi syndrome is a genetic disorder due to the lack of expression of paternal genes on chromosome 15q11-13 region. Clinical manifestations include neonatal hypotony, hyperphagia, obesity, hypogonadism and a intellectual disability in variable grade. Nonetheless, an important percentage of cases defined as Prader Willi like syndrome is suspected there is not a genotype/phenotype correlation. **Objective:** To describe the genetic findings in patients with Prader Willi phenotype lacking any alterations in region 15q11-13.

Methods: We studied 62 patients with Prader Willi syndrome phenotype by karyotype, FISH and PCR-based methylation test. A search for cases published during the period 2005-2018 was performed. Selection included the Pubmed database (www.pubmed.com) and Scielo (www.scielo.br). Those cases where karyotype, FISH, PCR-based methylation test and CGH failed to confirm the clinical diagnosis were selected and compared with the results of patients included in our study.

Results: International scientific literature reports until 80% of diagnosed cases as Prader Willi like syndrome. Chromosomal alterations involve the following chromosomal regions: 6q, Xq, 10q, 12q, 1p, 2p, molecular pattern compatible with Angelman's syndrome and maternal uniparental disomy in chromosome 14. It was observed 50% of cases in our investigation with Prader Willi like syndrome, without alterations seen by classical cytogenetic.

Conclusions: Lack of confirmation for a chromosomal region 15q11-13 alteration makes a deep clinical delineation, classical cytogenetic test and molecular studies throughout the genome are powerful tools indispensable for genetic diagnosis in patients with a Prader Willi like syndrome.

Poster #7 International Prader-Willi Syndrome Free Diagnosis Programme

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Prader-Willi syndrome (PWS) is a rare genetic disease where an early diagnosis can have a significant impact on the life expectancy of the patient. Whilst there are specific pharmacological treatments that can improve the quality of life of PWS patients, like hormone replacement therapy, the most important part of the therapy is appropriate dietary restrictions. Diet alone can significantly improve the life expectancy in PWS patients and it can be implemented regardless of the socio-economic conditions. This is why we need to make sure that every child with PWS has a confirmed diagnosis as early as possible.

Since 2004 the "Mauro Baschirotto" Institute for Rare Diseases (BIRD), together with the International Prader-Willi Syndrome Organisation (IPWSO), offers free diagnostic tests for PWS for the countries where such service is not currently available. This experimental program is intended as a means for medical doctors to molecularly confirm or eliminate the clinical diagnosis of PWS in their patients.

Since the beginning of this initiative 530 samples from 44 different countries have been analyzed, identifying 192 cases of PWS. The analyses use the methylation specific polymerase chain reaction (MS-PCR) method and the sample sending procedure was designed to be as straightforward as possible using dried blood spots (DBS) on Whatman type filter paper. In addition to this testing, the laboratory at BIRD has trained two laboratory directors in the use of the testing methodology so that they may introduce testing in their own country.

The initial procedure relied purely on the referring medical doctor to determine the suspected cases but the resulting percentage of positives was below our set goal of 40% (33% in 2005). During the ensuing years various steps were introduced to help in the clinical diagnosis and improve the selection of the most likely cases of PWS. This resulted in the increase of positives to more than 40% (54% in 2018). The current procedure includes a clinical data collection form and a pre-approval step before a sample can be accepted for testing. The data collection form includes the international guidelines for the clinical diagnosis of PWS and contains fields for key information that can help in the diagnosis of PWS.

An ongoing project is the adaptation of the methylation specific multiplex ligation-dependent probe amplification (MS-MLPA) method for international PWS testing, with an aid from MRC Holland, the company that developed and produces the PWS MS-MLPA diagnostic kit. In comparison to the currently used MS-PCR method, MS-MLPA allows the discrimination between deletion and non-deletion subjects with PWS. In addition, this test can also give an estimate of the size of a deletion. Special focus is given to the quality of the samples and the DNA extraction method, as MS-MLPA is very sensitive to variations between the tested DNA samples and the calibration controls.

Additional efforts will be made to raise awareness of this initiative to as many people as possible. The guidelines are being further improved and a new separate documentation specifically aimed at families is being introduced to help them understand the importance of these tests for the health of their loved ones with PWS.

Poster #8 Investigating the contribution of the Prader-Willi syndrome critical interval to behaviour and cognition

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Introduction: The core features of Prader-Willi Syndrome (PWS) are hypotonia and slow growth rate in infancy, followed by severe hyperphagia, which can lead to obesity throughout childhood and adulthood. Individuals with PWS also exhibit mild to moderate learning disability as well as a range of behavioural and psychiatric phenotypes suggestive of elevated anxiety, impaired attention, and psychosis.

PWS is caused by loss of function mutations affecting paternal expression of genes from the imprinted cluster on chromosome 15q11.2-q13. Two non-coding RNAs, *SNORD116* and *IPW* within this cluster are collectively known as the PWS critical region (PWS-cr), as deletion of the PWS-cr is sufficient to lead to PWS. However, while PWS-cr contributes heavily to the core features of PWS, including the hyperphagia and hypotonia, it is unclear whether, and to what extent, it plays a role in the behavioural and psychiatric phenotypes typical of the syndrome. Our previous studies of a full genetic mouse model for PWS (PWS-IC) shows deficits in endophenotypes of relevance to the behavioural and psychiatric problems, including hypoactivity, sensory-motor gating, attention, and impulsivity. The aim of this study is to characterize the behaviour of a PWS-cr^{+/-} mouse model in order to assess whether the PWS-cr plays a role in the manifestation of these behavioural and cognitive abnormalities.

Methods: PWS-cr^{+/-} mice were assessed as adults (8-weeks onwards) on measures of locomotor activity, anxiety (open field and elevated plus maze), sensory motor-gating (acoustic startle and prepulse inhibition tests). The 5-choice serial-reaction time task (5CSRTT) was used to assess attention and impulsivity. An RNA sequencing study on brain tissue from the PWS-cr^{+/-} mouse model is being performed in order to examine the effect of PWS-cr on gene expression and post-transcriptional modifications in the brain.

Results: Loss of the PWS-cr led to some subtle behavioural changes. While there was no difference in behaviour between genotypes on the elevated plus maze, the results from the open field were suggestive of elevated anxiety in the PWS-cr^{+/-} mice. No differences between genotypes were found in locomotor activity or in habituation to the environment. The PWS-cr^{+/-} mice also exhibited reduced acoustic startle response compared to wildtype, but no differences in pre-pulse inhibition of the startle response. Results from the 5CSRTT indicated no effect of genotype on attention, but indications of defective learning and increased impulsivity in the PWS-cr^{+/-} mice.

Conclusions: Overall, the PWS-cr^{+/-} mice exhibited elevated anxiety, reduced acoustic startle response and increased impulsivity. However, the absence of the PWS-cr interval did not have an effect on locomotor activity, attention and pre-pulse inhibition. This is in contrast to the behavioural profile of the “full” genetic PWS-IC mouse model. These results suggest that whilst the PWS-cr interval might play a subtle role in some of the behavioural phenotypes seen in PWS, it does not lead to the behavioural and cognitive endophenotypes associated with psychiatric illness seen in a “full” genetic mouse model for PWS.

II. Endocrinology

Poster #9 Serum concentrations of asprosin in children Prader-Willi syndrome: association with glucose and insulin resistance

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Introduction: Asprosin is a newly discovered hormone produced by the white adipose tissue that stimulates glucose production and is correlated with insulin resistance. Asprosin increases after fasting and decreases with food intake, utilizing the same signaling pathways, Neuropeptide Y/Agouti-Related Peptide (NPY/AGRP), as ghrelin. Both asprosin and ghrelin are orexigenic hormones. Prader-Willi syndrome (PWS) is a unique clinical model of disordered satiety and paradoxical hyperghrelinemia. However, it is not clear if asprosin levels are altered in children with PWS. Therefore, the aim of our study was to measure the concentrations of serum asprosin in children with PWS and BMI-z score matched children and to assess its relationship to glucose, insulin resistance, ghrelin, leptin, and percentage of body fat.

Methods: Fasting and 1-hour post meal serum concentrations of asprosin were measured using an enzyme-linked immunosorbent assay kit (Catalogue No. abx257694; abbexa, Cambridge, UK) in ten children with PWS (9F/1M, 5.1-17.9 years) and seven BMI-z score matched children (1F/6M, 6.8-17.1 years). Hormones including: glucose, insulin, acyl ghrelin and leptin were also measured. Height was measured to the nearest 0.1cm using a wall-mounted stadiometer and weight was measured to the nearest 0.1kg using the calibrated scale. Body composition (percent body fat) was measured by air displacement plethysmography. Homeostatic model assessment insulin resistance (HOMA-IR) was calculated as fasting glucose (mg/dL) × fasting insulin (μIU/mL) ÷ 405. Groups were compared for %fat, fasting and 1 hour level of hormones using the Mann-Whitney U Test; Wilcoxon Signed-Rank Test was used for within group comparison of fasting asprosin and 1-hour post meal asprosin. Correlation between each fasting and post-meal asprosin, demographic and other fasting hormone levels were determined using Spearman's Rank-Order correlation, considering a critical significance value of $p < 0.05$.

Results: PWS and controls were of similar age and BMI-z score. Children with PWS had lower fasting levels of glucose ($p = 0.04$) and showed a trend for lower HOMA-IR ($p = 0.05$). Fasting asprosin, insulin, percent body fat and leptin were comparable between groups. However, children with PWS had higher fasting levels of acyl ghrelin ($p = 0.02$) compared to BMI-z score matched children. Fasting asprosin and 1-hour post meal asprosin did not differ between children with PWS and BMI-z matched children ($p = 0.37$ and $p = 0.5$, respectively). Fasting asprosin was positively associated with percent body fat and BMI-z score ($r_s = 0.70$, $p = 0.04$ and $r_s = 0.90$, $p < 0.01$) in children with PWS, but not in BMI-z score matched children.

Conclusion: This study indicates that fasting acyl ghrelin is higher and fasting glucose is lower while HOMA-IR trend to be lower in children with PWS, suggesting that children with PWS are more insulin sensitive than BMI-z score matched children. Serum asprosin was positively associated with adiposity-related parameters in children with PWS, including

percent body fat and BMI-z score; no significant correlations were found in controls. Future larger-scale studies in children with PWS and obesity (with and without insulin resistance) is needed to confirm our findings.

Poster #10 GH stimulated levels during transition phase in Prader-Willi syndrome

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Introduction: In the general population, GH deficiency (GHD) during the transition phase is associated with deterioration of body composition, metabolic alterations and reduced bone mineral density. Subjects with Prader-Willi syndrome (PWS) have reduced muscle mass, increased risk of cardiovascular disease and osteoporosis, similarly to what has been observed in patients with non-syndromal GHD. Consequently, assessment of the GH status from late teenage years until 6-7 years after achievement of final height may be particularly helpful in the management of PWS in this particular period.

Methods: A cross-sectional study was performed in 133 patients with genetically-confirmed PWS (85 del15, 46 UPD15, 1 ID, 1 met+), 69 females, aged 19.8±2.4 yr (mean±SD), BMI 35.6±10.4. Ninety-three subjects had previously undergone GH treatment (69.9%), and withdrawn in all cases at least 6 months before starting the study protocol. Pituitary GH secretion was evaluated by standard dynamic testing with GHRH+arginine. In order to define GHD, we adopted the BMI-related diagnostic cut-off limits of GH peak (GHp) (Corneli et al, Eur J Endocrinol 2005). In addition, the cut-off limit specific for transition phase (GHp <19 µg/L) (Corneli et al, Eur J Endocrinol 2007) was used. Serum IGF-I levels were determined at baseline.

Results: According to the BMI cut-off limits, 31 of 84 (36.9%) obese (BMI= 44.6±6.7) PWS subjects could be defined as GHD (GHp<4.2 µg/L), as well as 7 of 24 (29.2%) overweight (BMI= 27.6±1.4) patients (GHp<8 µg/L) and 5 out of 25 (20.0%) normal weight (BMI= 22.4±2.2) individuals (GHp<11.5 µg/L). Overall, GHD was present in 32.3% of the subjects. Serum IGF-I was <-2 standard deviation scores (SDS) in 51 patients (38.3%). Twenty-five subjects had both the pathological GHp and IGF-I <-2 SDS (18.8%). Finally, 99 individuals showed GHp <19 µg/L (74.4%).

Conclusion: Our results indicate that GHD may be present in a significant percentage of PWS patients during transition phase. The challenge is to demonstrate that GH therapy after completion of linear growth will lead to an improvement in morbidity and mortality in PWS individuals. Thus, a re-evaluation of the GH secretory pattern may be beneficial in all PWS patients after achievement of final height.

Poster #11 Effect of Growth Hormone Treatment on Glucose Tolerance in Young Adults with Prader-Willi Syndrome

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Introduction: in children with Prader-Willi syndrome (PWS), the benefits of growth hormone (GH) treatment are well established. GH has substantially changed the phenotype of children with PWS. Currently, when young adults with PWS have attained adult height (AH), they have to stop GH treatment. Adults with PWS are predisposed to develop impaired glucose tolerance (IGT) and diabetes mellitus type 2 (T2DM). Reports on the prevalence of T2DM vary from 7-24% in adults with PWS. Studies in adults with PWS showed positive effects of GH on body composition and metabolic health parameters, but GH is known to induce insulin resistance, which might lead to IGT and T2DM.

Methods: in this open-label, prospective study we investigated the effect of continuation of GH after AH attainment on glucose homeostasis in 42 young adults with PWS. All young adults received 2 years of GH after AH attainment in a standard dose of 0.33 mg/m²/day (~0.035 mg/kg/day). An oral glucose tolerance test (OGTT) was performed every year. IGT and T2DM were defined as glucose levels at 2 hours after glucose load between 7.8 and 11.0 or >11.0 mmol/l resp.

Results: there was no increase in plasma glucose and insulin levels or glucose AUC during 2 years of GH. Insulin AUC (30.2 to 38.6, p=0.047) and HOMA-IR (1.2 to 1.8, p=0.03) increased significantly during 2 years of GH. Since fasting glucose tended to be correlated with age and fasting insulin was correlated with BMI, results were corrected for age, sex and BMI. IGT was present in 8/42 after 2 years of GH, while not one patient developed T2DM.

Conclusions: 2 years of continuous GH treatment in young adults with Prader-Willi syndrome, who have been treated with GH during childhood for several years, does not impair glucose homeostasis and does not lead to T2DM.

Poster #12 Growth hormone treatment in adults with Prader-Willi syndrome has sustained positive effects on body composition

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Introduction: In children with Prader-Willi syndrome (PWS), the benefits of growth hormone (GH) treatment are well established. Several one year studies have shown that GH treatment is also beneficial for adults with PWS, improving body composition. However, little is known about the longer-term effects. The objective of this study is to investigate the effect on body composition after adult height (AH) attainment, of either continuation of GH for 2 years or restart of GH for 2 years after cessation for a median period of 1 year.

Methods: Open-label, prospective study in 53 young adults with PWS performed in a PWS Reference Center in the Netherlands. All young adults received at least 2 years of GH after attainment of AH in a standard dose of 0.33 mg/m²/day (\approx 0.035 mg/kg/day). A DXA scan was performed at baseline and at 1 and 2 years to assess fat mass percentage (FM%) SDS and Lean body mass (LBM) SDS.

Results: In 27 adults who continued GH, estimated mean (95% CI) FM% SDS did not change during 2 years of GH (2.1 (1.9 to 2.3) SDS at baseline vs. 2.2 (2.1 to 2.4) SDS after 2 years, $p=0.19$), neither did LBM SDS (-1.9 (-2.4 to -1.4) SDS vs. -1.8 (-2.3 to -1.5) SDS, $p=0.70$). In 26 adults who restarted GH, FM% SDS decreased significantly, from 2.2 (2.0 to 2.4) SDS to 1.9 (1.7 to 2.1) SDS, $p<0.001$, while total body LBM SDS increased significantly from -2.3 (-2.7 to -2.0) SDS to -1.9 (-2.2 to -1.5) SDS, $p<0.001$. There were no GH-related adverse events during the study.

Conclusions: Continuation of GH treatment for 2 years after AH attainment maintains the positive effects on body composition attained during childhood, while restart of GH after discontinuation for 1 year improves body composition. Thus, adults with PWS benefit from longer-term GH treatment.

Poster #13 Effects of growth hormone treatment on thyroid function in pediatric patients with Prader-Willi syndrome

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Introduction: It is unclear whether hypothyroidism is present in patients with Prader-Willi syndrome (PWS). This study aimed to clarify the state of the hypothalamic-pituitary-thyroid axis and the effects of growth hormone (GH) treatment on thyroid function in pediatric patients with PWS.

Methods: We retrospectively evaluated thyroid function in 51 patients with PWS before GH treatment using a thyroid-releasing hormone (TRH) stimulation test (29 males and 22 females; median age, 22 months). We also evaluated the effect of GH therapy on thyroid function by comparing serum fT3, fT4, and TSH levels at baseline, 1 year and 2 years after GH therapy.

Results: TSH, fT4, and fT3 levels were 2.28 (IQR; 1.19 to 3.61), 1.18 (IQR; 1.02 to 1.24), and 4.02 (IQR; 3.54 to 4.40), respectively. In 49 of 51 patients, the TSH response to TRH administration followed a typical pattern; in 2 patients (4.0%), the pattern suggested hypothalamic hypothyroidism (delayed TSH peak after TRH). TSH, fT4 and fT3 levels did not change significantly during 1 or 2 years after GH treatment.

Conclusions: The TSH response to TRH showed a normal pattern in most patients, and thyroid function did not change significantly during the 2 years after initiating of GH treatment.

Poster #14 Screening for Central Adrenal Insufficiency in Children with Prader-Willi-syndrome (PWS) with single collection of ACTH and Cortisol levels

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Background: Many of PWS features are explained by hypothalamic dysfunction, therefore these individuals are at high risk for pituitary hormonal deficiency. When the pituitary begins to fail, there is generally a specific sequential failure of pituitary hormones, starting with GH, continuing through LH and FSH deficiency, and culminating in loss of TSH and ACTH. A high prevalence (60%) of central adrenal insufficiency (CAI) however, has been reported in PWS using the metyrapone test. Many children, including infants have undergone stimulation testing to confirm or rule out CAI. Several studies however, using same test and other different testing methods including insulin tolerance test (ITT), low dose/high dose ACTH stimulation, glucagon stimulation tests have reported differing results with much lower rates of CAI ranging from 0 to 14% in PWS subjects. Previous study has shown that basal cortisol is closely correlated with adrenal response to stimulation.

Objectives: To assess single basal ACTH and Cortisol level as screening and prevent further stimulation testing for central adrenal insufficiency in children with PWS.

Methods: We studied 105 children (60 males and 45 females) with genetic diagnosis of PWS. Sixty eight (60 %) had deletion I and II, 24 (23%) UPD and 13 had only positive DNA Methylation testing. Plasma basal Cortisol and ACTH levels were collected between 7:30 and 8:00 am. All participants were 6 months to 9 years of age on GH treatment without illness or any other stressful condition during testing.

Results: All had normal morning Cortisol and ACTH level but 2 children, age 2 and 5 years with low and 4 y.o. male with increased cortisol level. These 3 children had normal ACTH level. Repeat sample after a week, revealed normal both Cortisol and ACTH level in all 3 children.

Conclusions: In this large number of children with PWS, we found no clinically significant cases of CAI after morning basal Cortisol and ACTH level, suggesting that CAI is rare in PWS. The true prevalence of CAI in the PWS population remains unclear and clinical assessment and diagnostic procedures to establish the need for replacement are still far from perfect. Screening with single morning Cortisol and ACTH, however could prevent further stimulation testing as well as unnecessary glucocorticoid replacement.

Poster #15 Central precocious puberty in a boy with Prader-Willi syndrome during growth hormone replacement therapy

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Introduction: Prader-Willi syndrome is a genetic disorder characterized by obesity, short stature, hypotonia and hypogonadism. Delayed or incomplete puberty are usually found in PWS, whereas central precocious puberty is very rare. This study aimed to report the case of a boy with PWS who was diagnosed with precocious puberty during growth hormone replacement therapy.

Methods: We retrospectively analyzed the genetics, clinical characteristics and laboratory findings of the boy.

Results: By the age of 4, the boy had mental retardation, epilepsy, characteristic face features, short stature with feeding difficulty in Neonate, and many clinical criteria of PWS diagnosis, which was confirmed by DNA methylation test (MS-MLPA) . Therapy with recombinant human growth hormone (rhGH) replacement (0.1 IU/kg/day) was started. 2 years later, he performed increased testicular volume and growth velocity, high testosterone levels and advanced bone age. An ACTH test yielded a normal response and A GnRH test showed premature activation of the hypothalamic-pituitary-gonadal axis with pubertal gonadotropin and testosterone levels (gonadotropin-releasing hormone stimulated LH peak 20.51 IU/L, testosterone 3.32 nmol/L). Magnetic resonance imaging (MRI) of hypothalamic-pituitary region was normal.

Conclusions: In PWS, puberty is usually delayed and secondary sexual characteristics are almost always incomplete. True precocious puberty is very rare and only a few cases have been reported. Our patient fulfilled all diagnostic criteria for CPP. The rare manifestations of CPP in patients with PWS has been attributed to brain lesions. We hypothesize that our patient's precocious puberty resulted from abnormal brain discharge caused by epilepsy. Next step, we will treat the patient with gonadotropin-releasing hormone analog (GnRHa) and follow up his pubertal development.

III. Gastrointestinal & Nutrition

Poster #16 Nutritional phases in 25 Chilean Prader-Willi Syndrome children: case series

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Introduction: Prader-Willi Syndrome (PWS) is the most common cause of genetic obese and hyperphagia is the key concept associated to this uncommon condition. Most pediatrician and dietitian are not aware of the nutritional phases of this syndrome. Hence, clinician suspicion could not be focused on a hypotonic undernourished infant with feeding difficulties or normal weight and regular feeding behavior toddler.

The aim of this study was to reproduce the nutritional phases on a Chilean serial cases. Methods: A cross sectional study of 25 children with PWS on nutritional control at Clinica Santa Maria, Santiago de Chile during 2017-2018 was done. Nutritional status assessment was made according World Health Organization references. The classification on nutritional phases was made by clinical history using Miller and cols criteria.

Results: 25 children from infants to adolescents were assessed. 24% were under 2 years old and all of them were on I phase and all of them were underweight, risk or normal weight. Among 2 to 5 years old children 75% were at phase 1b or 2a and 66% of the children were normal weight. Over 5 years old subgroup 71% were on 2b or 3 phase and the same percentage were overweight or obese. When performing Fisher statistical test was obtained a significant association between age and nutritional phases but not between age a nutritional status.

Conclusions: In our Chilean series there was a correlation between age and nutritional phases that could be helpful to convey to clinician implicated on the diagnosis.

Poster #17 Reflexive exploration of children with Prader-Willi syndrome eating habits

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Introduction: In Prader-Willi syndrome (PWS), eating disorders remain a major difficulty throughout their development. In the medical literature, the dietary problems/eating disorders of children and adolescents with PWS are addressed through four focal length: (1) nutritional phases (from feeding difficulties to hyperphagia); (2) eating behaviour, (3) pathophysiological aspects and (4) hormonal regulation. Thus, eating food habits have not been studied in terms of social determinants. That include the acquisition of social norms related to eating practices and table manners, food categories, neophobia behaviours and family interactions. In addition, available data are mainly obtained through the answers of parents or Carrers and not by a direct experimental observation.

Methods: The objective of this research program is to understand the eating practices of children aged 3rd to 18th in a "natural situation" by using an innovative method. Observations of family meals (n=15) will be carried out on the Ovalie platform, a modular observation platform - which in the case of this experiment will be used as a family dining room - equipped with data collection devices (cameras, directional microphones) controlled from a control room and backed by data collection and processing software (Emotion Facial Recognition, Social Interactions). The protocol will allow to replicate the context of family mealtimes by recreating conditions to those of the family. These filmed moments will be the subject of a "post-meal" reflexive screening and a double analysis: on the one hand, by the researchers to try to identify behavioural regularities and, on the other hand, by the individuals themselves, to explain their practices, based on collective reflexive interviews with family members.

Results: This innovative method allow to do a reflexive ethnography of the eating habits of children and adolescents with PWS in life contexts. The technical mechanism will be mobilized to study the influence of social and physical contexts on eating food habits. It will also allow facial recognition of taste emotions. By varying the social, family and cultural dimensions of the study population, this research will reveal the characteristics of eating practices considered socially "problematic". We will focus our analysis on the learning that takes place in a context of family consumption: table manners, body management at the table, social interactions. We will also study how parents regulate (obligation, negotiation or abandonment of social rules) these moments of collective mealtime.

Conclusions: The use of the Ovalie platform is part of a useful interscience approach to better describe, understand and explain food practices specific or not to PWS. The work

carried out will lead to proposals for concrete applications in terms of therapeutic education, services in the field of living environment and food in particular.

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Poster #18 Adolescence and Early Adulthood are critical times for weight gain in people with PWS

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Background: It is well established that late adolescence and early adulthood are critical times in the development of the behaviours and consequences associated with Prader Willi Syndrome(PWS). It has been reported that without appropriate structures in place from a young age, poor behaviours and lifestyle have the potential to impact not only on the people living with or supporting the affected individual but the person themselves.

Based on the estimated prevalence of PWS occurring of 1 in 15000-20000 live births there could be between 377 and 502 people with PWS in the state of New South Wales (NSW) Australia. In NSW there are limited options for help with management of people with PWS. One tertiary hospital childhood service only sees patients to the age of 12 while the other will see them to 18. Ours is the only clinic that manages patients with PWS after discharge from paediatric services. Transition to High School at 11-12 years of age and leaving High School (18-19 years of age) are often times of uncertainty and much change with the potential of greater access to food sources and money. It is also when young people with PWS want to seek more independence, which is particularly challenging for those afflicted with disease. This study aimed to look at whether age of referral into this clinical service made a difference to the weight progression over the following 10 years.

Methods: A retrospective analysis was conducted on patients who had attended the Royal Prince Alfred Hospital (RPAH) PWS clinic between 1991 and June 2019. Weight and waist were measured at each clinic visit. The cohort was divided into 2 specific age groups: age \geq 18 (Adult) on entry (post school) and $<$ 18 (Adolescent, school attenders). Percent weight change was determined for the following 10 years where data was available. Analysis was conducted using SPSS Version 18.

Results: 110 people with PWS have attended the clinic since its inception. There was data on 96 of the patients. 47% (n=45, 53% female) of patients first presented as adults and 53% (n=51, 45% female) were first assessed in adolescence. The mean age of the Adult group was 27.02 ± 8.5 yr, and the Adolescent group was 14.7 ± 2.1 years ($p < 0.001$). The Adult group weighed more 97.9 ± 26.1 kg vs 81.3 ± 27.8 kg ($p < 0.01$) and had larger waist circumferences 111.2 ± 18.5 cm vs 101.8 ± 19.3 cm ($p < 0.05$) on entry to the clinic. However the Adolescent group gained a greater percentage of weight at each year after entry for the 10 years analysed ($P < 0.05$).

Discussion: This analysis shows that late adolescence to early adulthood can be a critical time for weight gain. This is thought to occur because of increased socialisation, greater burden of care and increased food access during this period.

Conclusion: Late adolescence and early adulthood is a critical time and more interventions are needed to help with the management of people with PWS through this period.

Poster #19 A Real-World Analysis of Weight Change in Adolescents and Adults with PWS

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Introduction: Knowledge of how weight changes over time in the PWS population is important for understanding the contemporary natural history of the disorder as well as for assessing the impact of new treatments for hyperphagia.

Methods: We developed a text message-based, prospective cohort study of adolescents (12+) and adults with PWS to assess changes in weight and BMI over a six-month period in the 'real world' setting. Data was collected using a clinical mobile technology platform, and included gender, age, height and growth hormone (GH) therapy status at baseline. Weight was collected weekly while changes in height, living situation, access to food, activity level, and medication were collected at three-month intervals. For data analysis, repeated measures ANOVA and Cochran Mantel Haenzel tests were used for bivariate analysis, and generalized estimating equations were used for population-specific multivariable analysis.

Results: One hundred and sixty-five (165) individuals with PWS in the US and Canada enrolled in the study, with a mean age of 19.7 years old (range 12 - 48). Thirty-three percent of the individuals were normal weight, while 15% were overweight and 52% were obese. The majority of adolescents were currently on growth hormone replacement therapy (78%) whereas only 38% of adults (18+) were receiving growth hormone. There was considerable variability in weight across participants (weight range: 71.4 to 466 lbs), but most individuals maintained relatively stable weight (median change: +2.02%) and BMI (median change +1.03%) over the study period and changes in living situation, activity, food access, medication had limited impact. Multivariable analysis for weight as an outcome showed that time in the study (weight increases slightly over time), gender (females had lower weight than males), and percentage of life on GH therapy (weight decreases as percentage of life on GH increases) were statistically significant fixed effects. Percentage of life on GH therapy (BMI decreases as percentage of life on GH increases) was also a statistically significant fixed effect for BMI as an outcome.

Conclusions: Participants were highly compliant over the six months of this text-based study, suggesting that a mobile technology-based data collection was readily accepted and highly manageable. We anticipate that the results of this study can inform future clinical trials for hyperphagia/obesity related therapies and provide a basis for understanding how well new therapies work in the real-world setting.

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Poster #20 Lack of response to disgusting food in the hypothalamus and related structures in Prader-Willi syndrome

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Background: Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder characterized among other symptoms by marked hyperphagia and food foraging even in garbage.

Objective: To investigate, based on a putative abnormal neural processing of disgusting signals, the brain response to visual representations of disgusting food in PWS using functional MRI (fMRI).

Methods: Twenty-one genetically-confirmed PWS patients, 30 age- and sex-matched and 28 BMI-matched control subjects viewed a movie depicting disgusting food-related scenes interspersed with scenes of appetizing food while fMRI was acquired. Brain activation maps were compared between groups and correlated with disgust and hunger ratings.

Results: At the cortical level, the response to disgusting food representations in PWS patients was qualitatively similar to that of control subjects, albeit less extensive, and engaged brain regions typically related to visually-evoked disgust, such as the anterior insula/frontal operculum, the lateral frontal cortex and visual areas. By contrast, activation was almost absent in limbic structures directly concerned with the regulation of instinctive behaviour robustly activated in control subjects, such as the hypothalamus, amygdala/hippocampus and periaqueductal gray.

Conclusions: Our study provides novel insights into the neural substrates of appetite control in a genetically-mediated cause of obesity. The presence of significant cortical changes further indicates that PWS patients consciously process disgusting stimuli, but the virtual absence of response in deep, limbic structures suggests that disgusting signals do not adequately reach the primary brain system for the appetite control.

IV. General Medical Issues

Poster #21 Increasing physical activity in adult patients with Prader-Willi syndrome: effectiveness and transferability

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Introduction: Although physical activity (PA) is recognized as an essential component of the management of patients with Prader-Willi syndrome (PWS), most adult patients have insufficient level of PA. Day-to-day management of patients with PWS is particularly challenging and little is known about PA and sedentary patterns or the effect of PA interventions in these patients. The aims of this study were 1) to objectively quantify spontaneous PA and sedentary behavior using accelerometers in adults with PWS, 2) to evaluate the effectiveness and transferability of a home-based supervised exercise training program on habitual PA, physical function and body composition.

Methods: The study included adult women with PWS who received the PA intervention (PWS group) (NCT03673813). Subjects with PWS exercised at home, twice a week for 16 weeks, under the supervision of a specifically trained physical activity instructor. Each training session lasted one hour and was based on a combination of endurance and resistance training. In PWS group, body composition (DXA absorptiometry), physical activity (Actigraph accelerometers worn at the hip during 7 days outside of the exercise training program) and physical function (6- min walk test), were assessed before and after the PA intervention. Transferability of the program was assessed with the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework. Control women with common obesity matched on age and percent body fat (CON group) included in a study of our team (NCT01113996) were used for baseline comparison. They underwent the same assessments of body composition and habitual PA.

Results: Ten women with PWS (median [P25-P75] age: 29 years [24-33], body fat: 51.9 % [49.2-54.7] %) and 20 control women were included. Total physical activity was 37% lower in PWS group compared to CON group ($P < 0.05$). Sedentary time, especially in prolonged, uninterrupted sedentary bouts (≥ 30 min), was higher in PWS group. Participation to the exercise training program was excellent (median attendance: 32 [31-32] sessions). The program increased moderate-to-vigorous PA ($+11$ [13] $\text{min}\cdot\text{d}^{-1}$, $P < 0.05$) and walking capacity (mean [SD]: $+29$ [37] m, $P < 0.05$) but no effect was found on body composition or sedentary time.

Conclusions: Subjects with PWS are characterized by lower physical activity and more prolonged sedentary bouts. Supervised home-based exercise sessions are a feasible and effective strategy to improve physical activity and physical function in these patients, although body weight and body composition were not changed. This study shows the

adjunct value of including a supervised PA intervention in the clinical management of adult patients with PWS.

Poster #22 Iceberg alert: systematic screening reveals large number of undetected health problems in adults with Prader-Willi syndrome

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Introduction: In Prader-Willi Syndrome (PWS), up to 3% of patients die every year. In half of the patients, the cause of death is of cardiovascular origin and / or obesity-related. Cardiovascular problems have a multifactorial origin, most of which relate to an excess of energy intake, compared to energy expenditure. On the one hand, excess energy *intake* due to overeating can cause morbid obesity, leading to diabetes and secondary cardiovascular complications. On the other hand, energy *expenditure* is low due to low muscle mass, which can further deteriorate due to undetected hormone deficiencies (like hypogonadism, hypothyroidism and GH deficiency). On top of this, fatigue (due to undetected hormone and vitamin deficiencies) can reduce exercise tolerance, thereby further increasing obesity. Due to the behavioral phenotype of PWS (patients do not report pain and hardly ever complain about physical problems), hormone deficiencies and other comorbidities often remain unnoticed. Undetected co-morbidity can lead to medical complications, requiring admission to the hospital ward or intensive care unit. Systematic screening can prevent part of the personal and financial burden of undetected comorbidity. In order to reveal yet undetected health problems, we performed a systematic health screening among adults with PWS.

Methods: We systematically screened 106 adults with PWS (mean age 31.3 ± 12.0 y) for the presence of (undetected) health problems. Based on a medical questionnaire, medical file search, extensive interview, thorough physical examination and biochemical measurements we made an overview of the health problems already diagnosed and those detected by our systematic screening.

Results: We found a striking number of undetected and untreated health problems and health risks. Undetected health problems (like hypogonadism, diabetes, hypothyroidism and hypertension) were present in 69% of the patients. 37% even had multiple undetected health problems at the same time. The most common health problems were hypogonadism (100% in males and 78% in females), vitamin D deficiency (51%) and scoliosis (44%). We also found many untreated health risks: 30% of the patients was not on a diet and 20% exercised less than 30 minutes a day.

Conclusion: We detected a striking number of untreated health problems and health risks among adults with PWS which, if left untreated, can pose a serious health threat. Systematic screening is needed to detect these problems in an early phase. This will prevent complications and might even reduce mortality in this vulnerable patient population.

Poster #23 Causes of death in Prader-Willi syndrome: Lessons from 11 years' experience of a National reference center

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Introduction: In the last 20 years, substantial improvements have been made in the diagnosis, treatment, and management of patients with Prader-Willi syndrome (PWS). Few data on causes of death are available since those improvements were made. Our study described the causes of death among French patients with PWS over the first 11 years of experience of the nationwide French Reference Center for PWS (FRC-PWS).

Methods: The study population was patients with PWS who died in France between 2004 and 2014. Our study relied on two sources of mortality information at the national level: The French Epidemiological Centre for the Medical Causes of Death (CépiDc) Registry and the FRC-PWS database.

Causes of death were classified into seven categories: respiratory, cardiovascular, gastrointestinal, severe infection, sudden/unexplained, other causes, and unknown. Descriptive statistics were calculated separately for children (<18 years) and adults (≥18 years).

Results: One hundred and four deaths were identified in France from 2004 to 2014. The median age at death was 30 years, ranging from less than 1 month to 58 years. Seventeen deaths occurred in patients under 18 years, with 70% of them in children under 2 years. Respiratory causes accounted for more than 50% of the deaths in patients with PWS. Among adults, most of the deaths were triggered by a respiratory failure while the main cause of death was a respiratory infection among children. Both, cause and age of death did not significantly differ according to gender or genetic subtype. In those adult patients with data on obesity, 98% were reported to be obese. We found no significant difference in the causes of death in patients with and without GH treatment.

Conclusions: Patients with PWS die prematurely. The principal causes of death are respiratory-related for all ages and, in most adults secondary to the complications of obesity. Thus, obesity prevention and adequate management of respiratory problems are the two most important ways to lower the mortality rate in this population.

Poster #24 Evolution of the French database of children with Prader-Willi syndrome

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Introduction: The French Reference Centre (RC) for Prader-Willi Syndrome (PWS) labelled by the French Ministry of Health in 2004 began a national register of children with PWS in 2005. In 2008, a cohort study in the different competence centres has been implemented in order to create a national database (DB). This DB includes medical, socio-demographic and familial data of children and adolescents with PWS.

Methods: Since 2016, we decided to improve the DB by reviewing the different variables. We took the opportunity to develop a new DB on Access 2016. This new tool contains 414 variables that cover multiple domains: genetic diagnosis, familial data, pregnancy and neonatal period, auxological and biological measurements, comorbidities, treatments, reeducative care and education. The old data collected before 2016 (n=348 patients) were transferred into the new DB. Between January 2016 and June 2019, we collected new data in the different French centres.

Results: Among the 1372 patients identified by the RC, 534 children were included in the DB. The population is composed of 51.9% of boys and the median age is 9.94 years (0.46-17.99). 462 patients (86.5%) have complete genetic diagnosis: 54.1% paternal deletion, 42.4% maternal uniparental disomy 15, 1.5% imprinting defect and 1.9% other genetic forms such as translocations. Among the 250 patients with paternal deletion, 87 (35%) have a known genotype subtype: 25% type 1 (long) deletion; 69% type 2 (short) deletion; 5% atypical deletion. For the remaining 72 patients (13.5%), we only have abnormal methylation profile results. The age at diagnosis was available for 512 patients. 72.5% of them were diagnosed during the first month of life (0.1 to 1 month) and for infants born since 2014 this percentage increases to 80.8%. In 22.9%, diagnosis is made during the first year of life with a median age at diagnosis of 2 months.

95.9% of 507 patients (data available) were treated with growth hormone (GH). Children born before 2014 began GH treatment at the median age of 1.6 years (0.3 to 14.7 years, n=366) whereas children born during the five last years started at 11.3 months (n=107).

Conclusions: We have now a very large and complete database including 534 children. This DB covering different aspects of PWS clinical and social profiles could be a powerful tool for retrospective and prospective studies. The first analyses show that the median ages at diagnosis and at start of GH treatment, decreased over time. In addition to our register, we developed case report forms for newborns and deaths. In addition, a PWS biological bank

has been started since 2016 and to date samples from 185 patients included in the database are available.

Special thanks to Pfizer Laboratory and the French Prader-Willi Syndrome Association.

Poster #25 Deprivation and obesity in patients with PWS

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Introduction: The Toulouse center of the French Reference Centre for Prader-Willi Syndrome (PWS) labelled by the French Ministry of Health in 2004 identified 1372 patients, included 534 children in the database and regularly follow about 120 children with PWS per year most of them addressed from all over the country because of a severe phenotype. We want to understand the causes of the severe obesity we observed in this population and particularly the link between deprivation and obesity which has not been evaluated in this rare disease.

Methods: We used the 11 items EPICES questionnaire which evaluates the deprivation of the family and was validated in a large cohort of 197 389 persons. The higher the score, the more deprived the family is; a cutoff of 30 was used to define deprivation. We administered EPICES questionnaire to 147 families during hospitalization in our center and Dykens hyperphagia questionnaire (HQ) and HQ for clinical trials (HQ-CT) to 40 patients among them. BMI was collected in all the 147 patients

Results: EPICES score was obtained for 147 families and children were 51% male with a median age of 7 years ranging from 0.3 to 19. Prevalence of deprivation in the 147 families is 25.9% (N=38), lower than the French general population (35%). BMI expressed in Z-score was significantly higher in patients with deprivation than in patients without deprivation (0.3 vs 2.35 p<005 Mann-Whitney test). The prevalence of obesity (Z-score BMI >2) is significantly higher in patients with deprivation than in patients without deprivation (50% vs 26.6%, p=0.015 Fischer test). Prevalence of deprivation is higher in patients with obesity (39.6%) than in lean patients (19%). HQ total score (20 vs 18), and HQ-CT score (5 vs 4) were not significantly different in patients without deprivation (N=35) vs patients with deprivation (N=5).

Conclusions: Deprivation is associated with higher prevalence of obesity in children with PWS albeit no difference on the severity of hyperphagia. These families deserve more attention and adequate follow-up.

Poster #26 Application of the Evaluación Integral IDEAL® in a case of Prader-Willi Syndrome: A proposal based on the International Classification of Functioning, Disability and Health (ICF)

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Introduction: Children with PWS exhibit various clinical manifestations from the fetal and neonatal period that predispose them to neurodevelopmental, cognitive, physical and behavioral disorders. Our study propose the application of the Evaluación Integral IDEAL® in the case of a child diagnosed with PWS, which is a comprehensive assessment based on the International Classification of Functioning, Health and Disability -ICF-, that works as an interdisciplinary tool that assess, identifies and describes changes in the components of a person's functioning, in order to guide the professionals, user and their family to take concerted decisions regarding the necessary actions that must be taken for its integral approach.

Method: Single case study, carried out with a 4-year-old boy with a confirmed diagnosis of Prader-Willi syndrome. The Evaluación Integral IDEAL® was implemented to assess the functions and body structures, activities and participation in the case studied, and its operating profile was also defined. The strengths and limitations of an assessment tool based on the ICF in a PWS case are analyzed from the professionals' perspective.

Results: The application of the Evaluación Integral IDEAL® allowed to identify clinical parameters of the current condition of the child, assess the status of functions and body structures, the performance of activities and participation according to age, and identify environmental factors that can influence their functioning and development. The functioning profile contributes to prioritize the attention needs, to define the goals of the comprehensive rehabilitation process and the intervention actions. Having an instrument with universal qualifiers, favors the interaction and communication of the rehabilitation team and the interdisciplinary for the approach and follow-up of people with Prader-Willi Syndrome, who require differentiated and multidisciplinary care.

Conclusions: The CIF it is reference framework to develop tools to measure or assess individual functioning, applicable to different contexts and populations. The application of the Evaluación Integral IDEAL® in the case under study allowed the identification of the variants of the children's functioning, beyond the medical diagnosis and the deficiencies. The assessment based on the realization of activities and participation, is key to guide intervention actions from different areas. The use of universal descriptors and qualifiers favor teamwork and communication between professionals and institutions. These findings allow us to consider that the Evaluación Integral IDEAL® is an alternative for the comprehensive approach of people diagnosed with Prader-Willi Syndrome, that are over 4 years of age. As it is an assessment tool based on the ICF, its application can be useful in clinical contexts and extend to other areas related to the rehabilitation of people with PWS.

Poster #27 Prader-Willi syndrome. Presentation of a clinical case

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Background: Prader-Willi syndrome is a genetic disease characterized by obesity with hypotonia and hypogonadism and intellectual disability. With a frequency in general population 1 / 15,000 to 25,000 per live births. Most of them occur sporadically, where more than 70% of the cases are produced by deletions of paternal origin in the 15q11-q13 region, 28% of the cases by maternal uniparental disomies and less than 2% are caused by alterations of imprinting.

Objective: to describe the phenotypic characteristics of a sick adolescent with early diagnosis, adequate social and family stimulation.

Clinical case: male adolescent with 14 years obese, moderate intellectual disability, very small hands and feet, hypogonadism, hypotonia that improved with rehabilitation and physical exercises carried out with his family, with adequate social relationship and multidisciplinary monitoring.

Conclusions: highlight the value of early diagnosis and the intervention of several specialists, allowing to provide genetic counseling to guide families. Achieving through several actions together improve the language, which the hypotonia disappears, reaching an adequate school and social incorporation, which elevates their quality of life.

Poster #28 Cardiovascular autonomic regulation in Prader-Willi Syndrome

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Introduction: Patients with PWS have a higher cardiovascular (CV) risk but the underlying mechanisms are unclear – this may be favored by a dysfunction of the Autonomic Nervous System (ANS). However, data on CV regulation by ANS assessed by Heart Rate Variability (HRV) in PWS are inconsistent. In this study, we investigated HRV during sleep in a large cohort of young patients with PWS and in age-matched controls.

Methods: 57 children and adolescents aged from 1 to 18 years who underwent a polysomnography from September 2014 to January 2017 were included in this study: 37 patients with PWS (mean age 7.2 years, from 1.1 to 17.1, 18 female and 19 male) and 20 age-matched controls (mean age 8.5 years from 1.8 to 18.6, 11 female and 9 male). For patients with PWS, the genetic subtypes were a deletion in 20/37, a maternal disomy in 16/37 and 1 patient carried an imprinting defect. All patients were treated with growth hormone for a mean duration of 5.4 years. Sleep was monitored during a single night in the sleep unit (Natus equipment). Sleep stages, arousals and respiratory events were scored using standard criteria (AASM 2012). HRV was analyzed through Kubios software. We selected at least five minutes of ECG signal during each sleep stage. HRV was assessed both in time domain (SDNN, NN50 and RMSSD) and frequency domain (Energy in low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.40 Hz) bandwidths). The LF peak depend mainly on sympathetic components and HF peak reflects cardiac parasympathetic tone.

Results: The mean Heart Rate (HR) was significantly higher in PWS patients compared to controls in N2 and REM stages, and tended to be higher in N3 stage. Regarding time domain analysis, the RMSSD was significantly reduced in all sleep stages and the PNN50 was significantly reduced in N2 and REM stages, with a trend in N3 stage. Regarding the frequency domain analysis, a significant decrease in LF power during slow wave sleep was observed in PWS group compared to control group. HF power reflecting the parasympathetic tone was lower in PWS group but this trend was not significant.

Conclusion: This study showed an altered parasympathetic activity reflected by a reduction in pNN50 and RMSSD while HF power displayed a downward trend ($p=0.06$). This was also observed in dynamic evaluation of the ANS performed in patients with PWS aged more than 6 (18 of them were also included in the sleep study) (data not shown). For example, a reduced initial increase in HR with active standing (30/15 ratio) was observed in 9/19 patients (47%) compared to normal values. Our findings are in accordance with those of DiMario et al. (1994) who reported a decrease in HRV with deep breathing under parasympathetic influence. The decrease in LF power might reflect an associated decrease in sympathetic tone as shown by Purtell et al (2013) who reported a reduced LF HRV meal response in adults with PWS. These changes in ANS CV regulation may contribute to the increased cardiovascular risk in PWS. Additional studies are needed to further investigate the probably centrally mediated mechanisms.

Poster #29 Behaviors related to hyperphagia in the Argentine population with Prader Willi Syndrome: association with the time of attendance to a transdisciplinary treatment

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Introduction: Nutritional aspects of individuals with Prader Willi Syndrome (PWS) involve diverse characteristics including abnormal satiety mechanisms, hyperphagia (uncontrolled appetite), and compulsive food behaviors. Hyperphagia has an early onset during childhood and is related to a persistent search for food, which greatly increases the risk of obesity. We aim to evaluate related behaviors to hyperphagia in individuals with PWS, and its relationship with time assistance to a transdisciplinary treatment.

Methods: This is an ongoing study of non-experimental, correlational, cross-sectional design. The sample, so far, is comprised by 27 individuals with PWS between 3 and 42 years old. Most individuals (89%) regularly attend a transdisciplinary-approach treatment at the SPINE Foundation. Nutritional approach includes safety measures to limit food access, an adequate nutritional plan for the patient, and nutritional re-education for both the family and patient. We asked the families to answer the hyperphagia questionnaire (HQ-CT). This questionnaire involves 9 questions, with Likert-type options ranging from 0 to 4 (thus ranging from 0 to 36) according to frequency of occurrence. Higher scores on HQ-CT are related to more hyperphagia-related behaviors. We obtained a license through the Foundation for Prader-Willi Research for the use of the questionnaire.

Results: In the present study the mean of hyperphagia score was 7.1 ± 4.7 , with ranging from 0 to 19. If we consider each individual item, the highest scores were found in the item that asked about steal or obtain food in secret (1.4 ± 1.0). Furthermore we found a negative correlation between hyperphagia-related behaviors and time assistance to SPINE treatment ($r = -0.502$, $p = 0.008$).

Conclusions: Studying in detail hyperphagia-related behaviors in individuals with PWS is relevance to evaluate the efficacy of nutritional interventions. It also allow to identify possible critical points in the daily life of the patient, thus enabling improvements in the therapeutic approach. Our study demonstrated evidence of emerging efficacy related to a transdisciplinary-oriented approach towards the treatment of hyperphagia-related behaviors.

Poster #30 Clinical profile in adolescents and adults with Prader Willi Syndrome

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Introduction: Prader Willi Syndrome is a rare disease neurodevelopmental disorder caused by the lack of expression of a 15q11q13 gene. Although clinical manifestations of this syndrome have been studied, there are no such descriptions in the Argentine population, and neither in patients undergoing transdisciplinary treatment. Previous descriptions include infantile hypotonia, poor suction, alterations in development, short stature, hypogonadism and hypogonadism, hyperphagia and excessive weight gain, cognitive and behavioral problems including tantrums, skin-picking among others. This study aim to describe the clinical profile of the population of Argentina with SPW that attends treatment to Fundación SPINE (SPINE).

Methods: This is an ongoing research, with a descriptive, cross-sectional, non-experimental design. Participants in the sample will be approximately 23 patients with PWS, without growth hormone therapy, who are treated for SPINE. They will be evaluated with the following studies: Ambulatory Monitoring Blood Pressure, Holter Cardiac, Polysomnogram (PSG), Hepato Biliary Pancreatic Ultrasound (BPH) Total Body Bone Densitometry (BMD).

Results: At the moment we are preparing database to realize later the statistical analysis. The objective is to identify: sleep disorders, detection of cardiac affections, body composition and detection of abdominal pathology.

Conclusions: One of the main conclusions that it is proposed to reach in this study is to identify if there are differences between the clinical profile of the Argentine population with PWS and the previous clinical descriptions. We consider it important to take into account the complementary studies to be able to evaluate in a more exhaustive way the population with SPW without growth hormone therapy. We believe it is necessary to develop a protocol for clinical studies for all patients with this pathology.

Poster #31 Nurse experience with the venepuncture process of adult patients with Prader-Willi syndrome

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Background: Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder characterized by marked hyperphagia and morbid obesity, together with hormone deficiencies, abnormal behaviour in relation to food (obsessive thinking, food foraging, stealing, etc.). Veins in patients with PWS are difficult to find due to obesity and probably to generalised hypotonia including venous tone. Since treating a patient with PWS often requires the acquisition of blood samples, an experienced nurse is mandatory in the multidisciplinary team.

Objective: On the basis of our experience, we propose some recommendations to be taken into account for blood sample collection in adult patients with PWS.

Methods: Recommendations based on grade E of evidence

Results: The following items must be taken into account: Drink a lot of water the night before, come to hospital with clothes with warm long sleeves, use local heat with hot gel, gain her/his confidence, make her/him to be comfortable, use gloves and double tourniquet 5-10 cm above venipuncture site, use alcohol pads in order to dilate the veins, use butterfly as needles, put all the tubes to be filled near in order of priority, just in case you cannot get enough blood for all. If blood does not come out, put the arm below heart level or raise the forearm or turn the wrist so as to get more circulating blood. If you cannot get a good vein, then proceed to artery puncture (radial). Remember that they do not feel pain (high threshold) or if the patient is afraid of feeling pain, use lidocaine cream. Put an adhesive pressure strip. Use biohazard waste container. Finally, do not forget to draw and keep a map of good veins for every patient so as to check next time she/he comes.

Conclusions: Following a nurse protocol for blood collection and other care issues in adult patients with PWS is essential for the best achievement of clinical assays, investigational projects and also the routine clinical care.

Poster #32 PATH for PWS Study: A Non-Interventional, Observational, Natural History Study of Serious Medical Events in Prader-Willi Syndrome

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Introduction/Background: The incidence of serious medical events in individuals with Prader-Willi syndrome (PWS) is largely unknown. The PATH (Paving the way for Advances in Treatments and Health) for PWS natural history study is being conducted to increase our understanding of the profile of medical events and behaviors associated with PWS, help contextualize observations in clinical trials, and aid in development of new therapies for treatment of PWS. PATH for PWS is sponsored by Zafgen, Inc. and the Foundation for Prader-Willi Research (FPWR) and is hosted by the National Organization of Rare Disorders (NORD).

Methods: This 4-year prospective longitudinal study was designed to advance understanding of medical history and events in participants with PWS. The primary objective is to identify the incidence of serious medical events (ie, any event resulting in death, is life-threatening, requires hospitalization or emergency room visit, or is medically significant) in participants with PWS. Additional objectives are to prospectively evaluate other medical outcomes, including the incidence of medical events of special interest (eg, non-serious thrombotic events), and prescription medication use associated with reported medical events. PWS-related questionnaires include the Hyperphagia Questionnaire for Clinical Trials, Food Safety Zone, PWS Profile, and Food Behavior Survey.

Results/Discussion: The study enrolled 700 volunteers ≥ 5 years of age in the United States, Canada, Australia, and New Zealand. Of these, 231 were 5-11 years of age 191 participants were 12-17 years and 278 participants were ≥ 18 years. A subset of participants (301 enrolled) provided a blood sample to measure D-dimer levels. A summary of study progress will be presented.

Poster #33 Morbidity and mortality in Prader-Willi Syndrome: implications for clinical practice

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Introduction: Prader-Willi Syndrome is a complex genetic condition that manifests often with behavioural difficulties and physical morbidity in childhood. It is characterised by deregulated eating behaviour, hyperphagia and often mild to moderate intellectual impairment. There is a lack of international consensus on how to manage and treat patients with Prader-Willi Syndrome.

Methods: A systematic review was carried out to examine the Medline, Cochrane, PsychINFO, CINAHL, Web of Science and Scopus databases for published material in the field of Prader-Willi Syndrome and hyperphagia. We were interested in any published morbidity and mortality data related to the hyperphagia phenomenon in PWS.

Results: Our systematic literature search resulted in 1384 papers identified as significant to the topic. The abstracts from these papers were reviewed by two independent reviewers, and 270 were judged to meet our inclusion criteria. Of these papers 243 were evaluated by their full text. Morbid obesity, type 2 diabetes mellitus, obstructive sleep apnoea, respiratory failure and hypertension were all regularly listed as significant problems in the literature reviewed. A number of papers also listed more unusual sequelae secondary to the hyperphagia phenomenon in PWS, such as choking or gastric dilatation and perforation. There is a high mortality rate, with one study finding a mean age of death of 29.5+/- 16 years*.

Conclusions: Prader Willi syndrome is highly associated with increased obesity and associated morbidity related to this. Understanding the risks involved informs management decisions. More research would also benefit the management of Prader-Willi Syndrome and improve our understanding of its associated morbidity and mortality.

*Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. *Genet Med.* 2017;19(6):635–642. doi:10.1038/gim.2016.178.

Poster #34 Prader-Willi Syndrome and hyperphagia: what is known about treatment and prevention?

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Introduction: Prader-Willi Syndrome is a rare and complex genetic condition that often manifests with a wide range of behavioural problems and learning difficulties in childhood. Patients are especially prone to excessive overeating, as well as food hoarding and stealing phenomena. It is a multifaceted and challenging syndrome to manage and there is a lack of international consensus as to how to manage hyperphagia in PWS.

Methods: Our review examined the Medline, Cochrane, PsychINFO, CINAHL, Web of Science and Scopus databases looking for published material in the field of Prader-Willi Syndrome and hyperphagia. We were interested in any published management strategies related to the hyperphagia phenomenon in PWS.

Results: Our systematic literature search resulted in 1384 papers identified as significant to the topic. The abstracts from these papers were reviewed by two independent reviewers, and 270 were judged to meet our inclusion criteria. Of these papers 243 were evaluated by their full text. Several different management strategies featured in our review, but we could broadly group them into three main categories: 1) medication including psychiatric treatments and endocrine treatments, 2) surgical intervention and 3) specialised MDT programmes, combining a calorie restricted diet with exercise and activities, often in a residential setting.

Conclusions: An MDT approach was frequently utilised in this complex syndrome with success. Residential programmes were also broadly successful in managing hyperphagia and weight gain in the syndrome, however the ethical questions around these still remain pertinent. More research would be beneficial to this evolving field of study and better help to inform management.

Poster #35 Improving care of Prader-Willi syndrome: Evaluation of a new care program combining Adapted Physical Activity, Nutrition and Therapeutic Education

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Introduction: Prader-Willi syndrome (PWS) is a rare and complex genetic disease characterized by hypothalamic-pituitary axis dysfunction combining eating disorders associated with hyperphagia and satiety deficiency, mild intellectual deficit and behavioral disorders. This disease requires continuous management through specific therapeutic education to prevent metabolic and cardiorespiratory complications related to obesity. Physical activity must therefore be regular, adapted to the disability, taking into account cognitive deficits and behavioral disorders. The presented study aimed to evaluate an innovative and individualized care program combining Physical activity, Nutrition and therapeutic education for adults with PWS who have been admitted to our hospital for 1 month.

Methods: Twenty-one adults PWS patients, 16 females and 8 males (median age: 30.4 years [min 20.8-max 58.1]; median BMI 47.3 kg/m² [min 26.6-max 68.3]) admitted to our hospital were enrolled in this study. The program includes: 2 days of assessments allowing the medicine to prescribe a physical activity program adapted to the patient's phenotypic profile, based on indoor or pool sports or physiotherapy sessions. For 4 weeks, patients, in addition to their physical activity program, will benefit from group workshops on nutrition and physical activity, and meal simulations to assess eating behavior. After the 4-week program, patients are reassessed to measure their physical and functional abilities and metabolic parameters. The benefits of the program on eating behavior, observance of the program and on the weight curve is also measured.

Results: The results showed, after the program, an improvement in physical abilities (6-minute walk test: +9.5%) and respiratory parameters (+ 8%), an interesting weight loss (-3.7% of BMI) and a good observance of the physical activity program (90.5% of the patients). However, the eating behavior does not show any significant improvement with the evaluation grid used. It seems that this would require more group workshop sessions.

Conclusion: This study demonstrated that an innovative and individualized care program combining Physical activity, Nutrition and therapeutic education for adults with PWS can lead to significant improvement in various clinical and behavioral parameters. However, these preliminary results should be confirmed by a double-blind randomized study with a larger number of participants.

Poster #36 Translational Research tools to Accelerate Therapeutic Development for PWS

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Introduction: There are several challenges to the current therapeutic development pipeline for PWS. The fundamental genetic and pathophysiological mechanisms underlying PWS phenotypes and cellular phenotypes are unknown, making target identification difficult. The paucity of patients, the limited knowledge on the natural history of PWS, the lack of biomarkers and patient-centric outcome measures of treatment efficacy, the limitations related to the predictive validity of animal models - the extent to which the model predicts clinical efficacy - impede translational research and slow therapeutic development for PWS. In this context, the Foundation for Prader-Willi Research (FPWR) has developed several programs in collaboration with stakeholders from industry, academia and other patient organizations at the international level to overcome key barriers along the therapeutic development path for PWS.

Programs: I will discuss the goals, progress and achievements of the following programs:

- The PWS iPSCs biobank was launched in 2018 thanks to the partnership between FPWR and the University of Connecticut-Wesleyan University Stem Cell Core to develop a centralized high-quality biobank of iPSC lines derived from individuals with PWS. These lines are available for academia and industry worldwide.
- A partnership with the Autism Brain Network has been established in 2017 to streamline brain donation process for families, and enhance the collection and distribution of high-quality post-mortem tissue to researchers.
- The PWS Pre-Clinical Animal Network was launched in 2016 to develop new models, validate pre-clinical mouse models of PWS and create a preclinical drug screening platform.
- The International Consortium to Advance Clinical Trials for PWS composed of stakeholders from industry, academia, and patient organizations was established in 2015 to address clinical trial challenges for PWS. The consortium aims to develop outcome measures to assess treatment efficacy against hyperphagia and other behavioral challenges, and patient- and caregiver-focused benefit/risk assessment of new treatments.
- The Global PWS Registry was developed in 2015 by FPWR in collaboration with international stakeholders in the PWS community to build a comprehensive clinical database to better understand the natural history and full spectrum of PWS characteristics, facilitate clinical trial recruitment and enrollment, and foster clinical research through the availability of de-identified and aggregated data to academic and industry collaborators.

Conclusion: Implementation of patient-centric, collaborative and international programs integrating the expertise of multiple stakeholders across the therapeutic development path are key to streamline, de-risk and accelerate therapeutic development for PWS.

Acknowledgements: I would like to thank the many contributors to these initiatives, including members of FPWR Research team, the PWS-Clinical Trial Consortium members, the PCAN members, the PWS Global Registry members, numerous individual scientists and clinicians who provided guidance, and all the patients and families who participated in many studies.

Poster #37 Prevalence of Prader Willi Syndrome in Pinar del Rio province after DNA methylation analysis introduction

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Introduction: Prader-Willi syndrome is a genetic disorder that requires molecular testing to confirmation of the diagnosis. Its early detection contributes to establish an individual management.

Objective: to describe the Prader Willi syndrome diagnosis results after DNA methylation testing introduction.

Method: A descriptive cross-sectional study was conducted in 13 patients with Prader-Willi suspect, who were followed in Pinar del Rio provincial office of Clinical Genetics during the last ten years. The results of chromosomal and molecular studies were considered and definite prevalence was calculated.

Results: At the beginning, 10 patients with Prader-Willy syndrome suspect were considered. Three of them (30%) showed a paternal chromosomal deletion of 15q11-q13 region. Others three patients (30%) only were confirmed with DNA methylation analysis, who may be caused of maternal uniparental disomy or imprinting defect. In rest patients (40%), the condition was refused. Across this investigation, three new cases were included. A complex chromosomal anomalies at chromosome 15 was identified in one of them and the others two children showed positive DNA methylation testing and paternal deletion of 15q11-q13 region. At moment, the prevalence is

Conclusions: DNA methylation specific testing is important to confirm the diagnosis of Prader-Willi syndrome. It is also useful to identify the genetic mechanism to study correlations phenotype- genotype for management and prognosis.

Poster #38 PWS in Brazil: follow-up in a reference center

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Introduction: In 2015 we started our PWS specialized outpatient clinic. In 2016, after IPWSO Conference, a group of parents began the PWS Brazilian Association which allowed a better information access and care. Other activities are made to develop the knowledge of PWS in our country, like conferences and contact with pediatric societies. This resulted in precocious diagnosis and new PWS patients that came for our clinic.

Objective: To analyze SPW patient's follow-up characteristics in 2019 compared with 2015.

Method: The inclusion criteria were PWS patients that were followed in Instituto da Criança-HCFMUSP from 0-32 years old. We evaluated the age of diagnosis; genetic type of PWS; age of follow-up started, Z-Stature-SDS, Z-BMI-SDS and growth hormone treatment. All patients received orientation in diet (900 calories/day independent of weight), physical activity and behavior. Our team is composed by pediatric endocrinologists, dieticians, nurses; psychiatric, neurologist specialized in sleep disorders and otorhinolaryngologist.

Results: We included 102 patients in 2019 (mean age:11.5±6.2y), and 51 patients in 2015 (mean age:10 ±6.5y). In 2019, 43% were deletion, 30,3% were maternal uniparental disomy, 2,9% had imprinting defects and 22,5% had only positive methylation test.

The age of diagnosis decreased from 3,43±3,28y to 2,8 ±3,3y, but the age of follow-up started was still high despite their reduction (4,95±4,26y to 4,5±4,1y). Also, we had a BMI improvement from 2,97 ±1,58SDS to +2,4 ±2,54SDS as in Z-Stature +1,41±1,52SDS to -1,22±1,33SDS. The incidence of obesity decreased from 72,9% for 60% in our patients. Regarding rhGH treatment, we had a great change. In 2015, only 29% of our patients were using growth hormone and this rises to 81,3% in 2019.

Conclusion: Our PWS specialized outpatient clinic could improve BMI-SDS and Z- Stature-SDS in a great number of patients. Indeed, more patients can have access to interdisciplinary team orientations and rhGH treatment. The precocious diagnosis and specially the start of a standard care were still important barriers for PWS in our hospital. The PWS association can help families to find information and refer for a specialized team.

Poster #39 Epidemiological aspect of scoliosis and bone mineral density in Taiwanese Patients with Prader-Willi Syndrome

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Introduction: Prader-Willi syndrome (PWS) is a genetic disorder that involves hyperphagia, obesity, hypogonadism, and short stature. The musculoskeletal manifestations includes laxity of ligaments, osteoporosis, and scoliosis. The purpose of this study is to assess the progression of scoliosis and bone mineral density of PWS patients in Taiwan

Methods: This was a retrospective study and chart review in which patients being diagnosed of PWS were recruited. Longitudinal follow-up of serial plain standing spine radiographs and dual energy X-ray absorptiometry (DEXA) were assessed.

Results: Thirty-four PWS patients, from 1 to 24 years of age, were collected, of which 16 patients were male and 18 patients were female. All patients were treated with growth hormone till the closure of epiphyseal plate. Thirty patients developed scoliosis (88%), in which two third had right major curve. Most of the deformities occurs at the thoracolumbar junction. For patients with scoliosis, the greatest Cobb's angle varied from 5 to 90 degrees with the mean angle of 18 degrees. Five patients (14.7%) had Cobb's angle more than 40 degrees. Only two patients received surgical treatment due to severe deformity. Interestingly, in our series, the severity of scoliosis is negative correlation with BMI.

The mean bone mineral density (BMD) in these patients increased as their age increased, from 0.545g/cm² at age of 2 to 1.043g/cm² at age of 23, but the Z-score seemed to decrease on the contrary, especially since their adolescence. The Z-score declined more rapid in females than in males.

Conclusions: PWS has several musculoskeletal manifestations during their lifetime, and scoliosis is one of the most frequently seen disorder. Although most of the cases do not need surgical correction, regular follow-up is still recommended since progression of the condition may occur. The Z-score of BMD decreased since their adolescence which implies the need for sex hormone replacement during these ages.

Poster #40 Characterization of Prader-Willi syndrome

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Introduction: Prader-Willi syndrome is a genetic disease characterized by hypotonia in childhood, hypogenitalism / hypogonadism, hyperphagia, obesity, variable intellectual disability.

Methods: four patients were studied are Prader-Willi syndrome, achieving clinical diagnosis, through the clinical or standard method.

Results: the four patients presented hypotonia in early childhood, retardation in psychomotor and language development. Obesity was presented as an infant, with a predilection of the trunk and avidity for food, hands and small feet, with short phalanges, hypogonadism improved with endocrinology treatment. The cognitive disability manifested in all patients was of a very variable degree.

Conclusions: the multidisciplinary monitoring of endocrines, physiatrists, speech therapists, defectologists and geneticists contribute to raising the quality of life of patients. Early specialized and family stimulation improves the school and social insertion of these patients.

V. General Medical Issues including Orthopaedics

Poster #41 Comparison of Hip and Knee Arthroplasty Rates of Individuals with and without Prader-Willi Syndrome

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Introduction: Prader-Willi syndrome (PWS) is a complex genetic condition, with a prevalence between 1:10,000 to 1:30,000. The prevalence of hip dysplasia in children with PWS is reportedly between 8% and 30%, but the consequences of their residual hip dysplasia is unknown. The purpose of this study was to comparatively estimate the number of total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures performed on adults with and without PWS, using a national hospital discharge database.

Methods: The National Inpatient Sample of the Healthcare Cost and Utilization Project is the largest all-payer inpatient care database, containing annual data from more than 7 million hospital stays; sampling weights and stratification variables are provided for producing estimates of more than 35 million hospitalizations nationwide. THA and TKA procedures were identified, then stratified by whether or not the patient had a diagnosis of PWS. The ages of the two groups and gender mix were compared, as was the length of stay for the procedure, and discharge status.

Results: From 2004 to 2014, 9.4 million patients nationwide, by weighted estimate, underwent THA (3.1 million) or TKA (6.3 million). Sixty-five patients were identified as having the diagnosis of PWS (39 with THA, 26 with TKA); seven patients per million having hip or knee arthroplasties had PWS. Sixty-eight percent of those with PWS were less than 50 years old, compared to only 7% of those without PWS ($p < 0.001$). The female:male prevalence was 47:53 for patients with PWS and 60:40 for the total group. The mean length of stay was similar, but patients with PWS were more likely to be transferred to another facility after surgery (77% versus 36%, $p = 0.008$).

Conclusions: Hip dysplasia prevalence is higher in persons with PWS, but the rate of late treatment with THA is much lower. We recommend active observation for the stable and improving hips, as the consequences of overtreatment of these children can be serious, including further delaying their neuromuscular development, or exposing them to possibly unnecessary peri-operative risks.

Level of Evidence: Nation-wide database analysis, Level III

Poster #42 Bone mineral density decrease in patients with Prader–Willi syndrome undergoing growth hormone therapy

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Introduction: Bone mineral density (BMD) is well known to decrease in adolescent and adult patients with Prader–Willi syndrome (PWS). Decreased BMD could be related to growth hormone (GH) deficiency and hypogonadism. Although studies have suggested that GH therapy improves BMD, we encountered some patients showing BMD reduction despite undergoing GH therapy. In the present study, we aimed to investigate the incidence of BMD decrease in PWS patients undergoing GH therapy from childhood to adolescent and whether there are sex differences in this reduction.

Methods and Results: Seventy patients (43 males and 27 females; age, 8–22.8 years; median age, 14.2 years) with PWS (deletion-type n=49, uniparental disomy-type, n=21) were examined. They had received, or were receiving GH therapy for >5 years (range, 5–14 years). We measured whole-body BMD by dual-energy X-ray absorptiometry, adjusting the BMD Z-score using patient height and age; patients with Cobb angle > 30° were excluded. Twenty patients [28.5%; 15 males (34.9%) and 5 females (18.5%)] showed a marked BMD reduction (adjusted Z-score < -2.5 SD) during the observation period, while 19 patients [27.1%; 11 males (25.6%) and 8 females (29.6%)] showed decreased BMD (-2.5 SD < adjusted Z score < -1.5 SD). There was a significant negative correlation between age and adjusted BMD Z-score, which began to decrease in early childhood and became prominent at pubertal age in both the sexes. The tendency of reduction, however, was more pronounced in males than in females.

Conclusions: In patients with PWS undergoing GH therapy, the incidence of marked BMD decrease was higher in males than in females, suggesting that it may be related with gender difference in hypogonadism. Although GH therapy was not sufficient to improve BMD, the incidence of BMD marked decrease could be reduced by this treatment.

Poster #43 Postural Assessment of the Spine and Lower Limbs in people with Prader Willi Syndrome

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Introduction: The present work aim to establish reference values of the different structural alterations of people with Prader Willi Syndrome (PWS), and to determine asociation between the severity of the spine deviations and the different imbalances that can be identified involving the lower limbs such as discrepancy of iliac crests and genu valgo.

Methods: We carried on a non-experimental, descriptive, cross-sectional study. All participants was evaluated with X-ray spinogram. The presence of scoliosis was determined and classified according to the region and affected areas, measured in degrees through Cobb angles. Using the same radiological study, the height difference of iliac crests was measured, drawing horizontal lines over each anterosuperior iliac spine, establishing the distance between both lines measured in millimeters. Furthermore, the extent of genu valgo was evaluated by means of the Morley classification, measuring the intra-malleolar distance in centimeters, and thereby reflecting the underlying severity. Spearman correlation coefficient was performed to assess correlations, and all statistical analyses were performed using SPSS software package.

Results: Main results showed valgus grade, acording to the Morley classification, 52% grade 2 (M = 4), 17% a grade 3 (M = 6.3), and a 30% grade 4 (M = 9.5). On the other hand 44% of patients had mild scoliosis (mean difference 9.2 mm), 6% had mixed mild / moderate scoliosis (mean difference of 20 mm), 31% had moderate scoliosis (mean difference 4.7 mm), 6.2% with mixed scoliosis (mean difference 5.5mm), and 6.2% with a severe grade (mean difference 12mm).

Within grade 2 genu valgo, 20% had mild scoliosis, 7% mixed, 20% moderate, and 7% had severe scoliosis. Among patients with grade 3 genu valgo, only 7% had moderate scoliosis; whereas within patients with grade 4 genu valgo, 27% had mild scoliosis, 7% moderate, and 7% mixed. Finally, using Spearman correlation coefficients, we did not identify significant relationships between the different variables explored.

Conclusions: In this study, we did not identify relationships between the severity or degree of the variables explored, thus corroborating the idiopathic nature of scoliosis, but leaving a space of uncertainty in its relationship with the different postural disorders of the lower limbs. Although we did not obtain the expected results, evaluation of the motor and postural approach is important in subjects with PWS from early age, since despite the most common practice involves only the evaluation of the spine, different lower limb imbalances can be found in these patients, forgetting the essentials of motor development in the first years of life..

VI. Clinical Trials for Hyperphagia and Behaviour

Poster #44 Chronic Treatment With Livoletide (AZP-531) Does Not Affect IGF-1 Plasma Levels: Preclinical and Clinical Results in People With Prader-Willi Syndrome (PWS)

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Introduction/Background: Patients with Prader-Willi syndrome have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG). These abnormalities in AG and UAG levels are hypothesized to be involved in the underlying mechanisms of hyperphagia. UAG is a 28-aa peptide that does not bind the growth hormone (GH) secretagogue receptor and has intrinsic activities that can counteract some effects of AG. Therapy with livoletide, a first-in-class 8-aa peptide analogue of UAG, is hypothesized to functionally correct the relative UAG deficiency to improve hyperphagia in people with PWS. In addition to hyperphagia, PWS is also characterized by dysregulation of the GH/insulin-like growth factor I (IGF-1) axis. GH therapy in PWS improves short stature, body composition, physical strength, and cognition. The objective of these investigations was to determine if livoletide affects levels of IGF-1 in rats and in people with PWS.

Methods: During a GLP 26-week toxicity study in 6-week-old rats, IGF-1 was measured (n=15/sex/group) on the last day of treatment with vehicle (VHL) and with livoletide at doses up to 45 mg/kg/day. Serum IGF-1 was also evaluated during a GLP rat juvenile toxicity study from post-natal day 21 to 86. IGF-1 was measured (n=16/sex/group) with VHL and with livoletide at doses up to 75 mg/kg/day. Tibia length and bone mineral density of the femur and lumbar vertebrae (L4-L6) were measured at the end of the treatment period in the VHL and 75 mg/kg/day livoletide group (n=10/sex/group). During a 14-day Phase 2a study, IGF-1 plasma levels were measured in 22 people with PWS (ages 13 to 46 years; 14M/8F) on day 1 and 14 of livoletide therapy (60 µg/kg/day). Six participants (4M/2F) were under GH treatment during the two-week treatment with livoletide.

Results/Discussion: In the 26-week study, livoletide treatment at dose levels up to 50-fold the highest intended human therapeutic dose did not affect the IGF-1 serum levels in either sex (M: 519.5±73.7 ng/mL VHL vs 513.6±75.6 ng/mL livoletide 45 mg/kg; F: 353.6±46.1 ng/mL VHL vs 338.5±60 ng/mL livoletide 45 mg/kg). In the rat juvenile study, 64 days of livoletide treatment also showed no effects on serum IGF-1 levels (M: 497.2±57.5 ng/mL VHL vs 520.1±79.6 ng/mL livoletide 75 mg/kg; F: 381.8±49.2 ng/mL VHL vs 388.6 ±71.8 ng/mL livoletide 75 mg/kg). Neither tibia length nor bone mineral density were affected by treatment with livoletide in the growing animals. In the Phase 2a study on day 1, PWS participants treated with GH (GHP) showed higher levels of IGF-1 when compared with non-GH treated participants (NGHP) (353.8± 129.7 ng/mL vs 162.2±59.6 ng/mL; p<0.005). After two weeks of treatment with livoletide, IGF-1 levels in both groups were unchanged compared with baseline (GHP: 341±164.3 vs 353.8±129.7 ng/mL; NGHP: 155.8±54.7 vs 162.2±59.6 ng/mL).

Conclusions: In both adult and juvenile rats, chronic treatment with livoletide does not affect circulating concentrations of IGF-1. Furthermore, a Phase 2a clinical trial showed no difference in circulating IGF-1 levels in people with PWS on GH therapy treated with

livoletide for 2 weeks. These results strongly suggest that livoletide does not impact the effects of GH in people with PWS.

Funding source: Millendo Therapeutics provided funding support for this study.

Poster #45 Nonclinical Development of Livoletide (AZP-531): A Peptide Analogue of Unacylated Ghrelin for the Treatment of Hyperphagia in Prader-Willi Syndrome

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Introduction/Background: Prader-Willi syndrome (PWS) is a rare, complex neurodevelopmental genetic disorder characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to a significant burden on patients and caregivers. There are no approved treatments for hyperphagia in PWS. Patients with PWS have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG). These abnormalities in AG and UAG levels are hypothesized to be involved in the underlying mechanisms of hyperphagia.

UAG is a 28-amino-acid peptide that does not bind the growth hormone secretagogue receptor (GHSR), unlike AG. UAG has intrinsic central and peripheral effects that counteract the effects of AG and are exerted through a GHSR-independent mechanism. Livoletide is a cyclic 8-amino-acid analogue of UAG with improved plasma stability and pharmacokinetics that is being developed as a therapy for hyperphagia in people with PWS.

Methods: The objective of this nonclinical development program was to support the clinical development of livoletide, which includes a pivotal Phase 2b/3 clinical trial in patients with PWS initiated in early 2019. The program was designed to outline the safety pharmacology and the chronic toxicologic and toxicokinetic profile, and to identify parameters for clinical monitoring of potential adverse effects. Genotoxicity, safety pharmacology, reproductive toxicity, and repeat-dose 13-week toxicology studies were all completed. In the *in vivo* studies, livoletide was administered subcutaneously consistent with the clinical route of delivery.

Results/Discussion: Livoletide was not found to be cytotoxic or genotoxic in these studies. Safety pharmacology studies indicated no treatment-related effects on major physiological systems. Results from preliminary embryo-fetal developmental toxicity studies in rat and rabbit indicate that livoletide at high multiples of the anticipated human exposure is not associated with adverse maternal toxicity, embryo-fetal toxicity or teratogenic potential when administered throughout the period of organogenesis. Repeat-dose toxicity studies of up to 26 weeks in rats and 39 weeks in dogs demonstrate livoletide is very well-tolerated, with no evidence of systemic toxicity. Cumulative data from these studies suggest that livoletide has a favorable safety profile. The highest chronic doses tested were 45 mg/kg in rat and 30 mg/kg in dog and considered as the NOAELs. These dose levels provided AUC values of greater than 50-fold the intended clinical systemic exposure (~1200 ng·h/mL). No anti-livoletide antibodies were detected in any of the toxicology studies mentioned above.

Conclusions: These results demonstrated favorable long-term safety of livoletide in animal models and support the subcutaneous administration of the highest anticipated human clinical Phase 2b/3 study dose.

Funding source: Millendo Therapeutics provided funding support for this study.

Poster #46 Livoletide (AZP-531), an Unacylated Ghrelin Analogue, Improves Hyperphagia and Food-Related Behaviors Both in Obese and Non-Obese People With Prader-Willi Syndrome

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Introduction/Background: Prader-Willi syndrome (PWS) is a rare, complex neuro-developmental genetic disorder characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to a significant burden on patients and caregivers. While a significant proportion of people with PWS is obese (BMI ≥ 30 kg/m²), hyperphagia is observed in both obese and non-obese people with PWS. There is currently no approved treatment for hyperphagia in PWS. People with PWS have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG), a hormone which counteracts many of AG's effects. Livoletide (AZP-531) is a first-in-class UAG analogue that was previously shown to significantly improve hyperphagia, food-related behaviors, and metabolic parameters, and to be well-tolerated in a Phase 2a trial. [Allas S *et al.* (2018) PLoS ONE 13(1): e0190849]. Here we present additional analyses that examine the effects of livoletide in obese *versus* non-obese people with hyperphagia in PWS.

Method: The Phase 2a trial was a randomized, double-blind, placebo-controlled study which included 47 people with PWS (23 in the livoletide group and 24 in the placebo group). Participants received a single daily subcutaneous injection of livoletide or placebo during a 2-week treatment period. The study population was characterized based on the body mass index (BMI) classification: BMI ≥ 30 kg/m² (obese), BMI < 30 kg/m² (non-obese). The effect of livoletide on hyperphagia and food-related behaviors was assessed by the change from baseline in the 9-item Hyperphagia Questionnaire (HQ).

Results/Discussion: There was a total of 34 obese and 13 non-obese participants in the study. As expected, baseline BMI, body weight (BW) and waist circumference (WC) were significantly higher in obese compared to non-obese PWS participants (BMI: 42.6 ± 6.0 vs 26.1 ± 2.8 , BW: 103.5 ± 23.0 vs 68.5 ± 9.1 and WC: 118.3 ± 15.5 vs 91.8 ± 7.7 , respectively, $p < 0.0001$). There was no significant difference with respect to the male to female ratio and the deletion to non-deletion ratio between the 2 populations. Hyperphagia scores were similar at baseline between obese and non-obese participants (HQ score adjusted for 0 to 36 scale to reflect 9-item HQ-CT: 12.8 ± 7.0 vs 14.0 ± 7.8 , $p = 0.6083$, respectively). Fasting AG and UAG levels were lower in the obese vs. non-obese groups (AG: 93.6 ± 72.6 vs 122.1 ± 54.4 , $p = 0.0275$, UAG: 123.9 ± 87.2 vs 154.1 ± 62.6 , $p = 0.0219$, respectively). Livoletide-treated participants experienced similar improvements in hyperphagia and food-related behaviors as measured by the HQ whether they were obese or non-obese.

Conclusion: These results highlight the potential of livoletide for treating hyperphagia in both obese and non-obese people with PWS and hyperphagia. Livoletide is being investigated further in the ZEPHYR Phase 2b/3 trial, an ongoing pivotal study which will provide data on the long-term safety and efficacy of livoletide in the treatment of hyperphagia and food-related behaviors in people with PWS.

Funding source: Millendo Therapeutics provided funding support for this study.

VII. Mental Health, Behaviour & Cognition

Poster #47 Therapeutic approach of emotional competencies for children with Prader-Willi Syndrome: the EMOT programme

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Introduction: People with Prader Willi Syndrome (PWS) have great difficulties of social adaptation that could be explained by disturbances of emotional competencies (i.e. ability to use emotions daily). However, the lack of knowledge about the emotional functioning of PWS people - and even more about its development during childhood – makes their care more complex. A first study (related to a doctoral thesis work) showed that PWS children (aged from 5 to 10 years) presented a significant developmental delay in expression, identification, comprehension and regulation of emotions, which is not only due to intellectual disability. Based on these results, the objective is to present a new therapeutic intervention programme (EMOT programme) specifically designed to help PWS children improve their emotional competencies.

Method: Twenty-five French children with PWS aged 5 to 10 were included. Based on a therapeutic and integrative approach, the programme is implemented by one of the usual children's therapists for 6 weeks. The effect of the program is measured by analysing the evolution of children's emotional competencies between a pre-intervention assessment session and two post-intervention sessions (immediate and after 3 months).

Results: The results show that the EMOT programme allowed children who benefited from it to improve the majority of their emotional competencies, and thus reduce their developmental delay. We find that the beneficial effect decreases as the task becomes more complex and requires more cognitive, perceptual and linguistic skills.

Conclusions: This work sheds new light on the emotional functioning and development of PWS and shows the relevance of a focused intervention.

Poster #48 Sexual abuse in exchange for food in Prader-Willi Syndrome

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Introduction: Hyperphagia leading to morbid obesity is the most striking feature of Prader Willi syndrome (PWS). It is well known that PWS individuals often try to obtain food by begging, lying, stealing, or breaking into locked cabinets. Sexual abuse is common among populations with intellectual disabilities. Inappropriate sexual behavior in exchange for food in PWS has not been previously described. The aim of the study was to report and characterize sexual abuse in exchange for food in individuals with PWS and offer recommendations for prevention.

Methods: Demographic and medical data was collected from the files of all individuals (18 females /18 males, ages 12-44years) with a genetically confirmed PWS who live in residential homes designated specifically for this syndrome. In these hostels, individuals are under continuous supervision by trained staff. The main caregiver was interviewed for histories of sexual behavior and abuse.

Results: Nine individuals (5F/4M) ages (21-40years) from our cohort (n = 36) were exposed to sexual abuse (6 heterosexual and 3 homosexual). In 7/9 cases food reward was used by the perpetrator in order to attract his victim, although not always actually given. Age at sexual abuse ranged from 11-30 years. One girl suffered from abuse at the age of 11 and at an older age offered intimate touching in exchange for food. Most of the individuals did not disclose the event and five continued to initiate inappropriate sexual activity in order to obtain food.

Conclusion: Besides the high risk for sexual abuse present in populations with intellectual-developmental disabilities, individuals with PWS are at an additional risk due to their food-seeking behaviors. We report that 25% of adolescents and adults in our hostels suffered from sexual abuse, most of them in exchange for food. This assessment is most probably an underestimation due to unknown or unreported cases. Special programs and guidelines for sexual security with specific adjustments for the PWS population are mandatory.

Poster #49 Improvement of cognitive development in Prader-Willi syndrome patients with early GH treatment

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Introduction: Growth hormone therapy (GHT) in older patients with Prader-Willi syndrome (PWS) has demonstrated the benefit in growth hormone response, improvement in body composition, decline fat percentage, and increment lean body mass. However, studies for PWS infants receiving GHT are scarce, with an improvement in motor and cognitive development in addition to body composition has been reported. In this study, we wish to know if the early GHT in early infants with PWS also can have these benefits.

Methods: A retrospective case analysis for PWS patients who received GHT before 3 years of age from 4 medical centers was conducted. The dose of GHT was 0.035 mg/kg/day (0.5-1 mg/m²/day). Patient demographics, molecular diagnosis, age of GHT, dose of GHT, developmental quotient (DQ), growth before and after treatment were analyzed. Another 20 patients who received GHT later than 3 years of age were used as control.

Results: Total 32 cases were analyzed. Twenty cases were treated before 12 months old while 12 cases were treated during 12-36 months. The mean age of start treatment is 11.4±8.2 months old (range 0.73-35.1, median 10.3). The mean follow-up period is 15±34.8 years (range 0.22-119.58, median 4.13). Cognitive development (Cognitive DQ/FIQ) was 64.9±17.8 which was significant higher than the group treated greater later than 3 years old (48.0±8.7, p<0.001).

Conclusions: Early administration of GHT benefits cognitive development in PWS.

Poster #50 Application of Projective Techniques for the Therapeutic Approach of patients with Prader Willi Syndrome

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Introduction: The objective of this work is to analyze the usefulness of graphic techniques (drawing) as a therapeutic tool to know characteristics in behavior, allow the expression of emotions and behaviors, which are difficult to explain and externalize verbally in people with Prader Willi Syndrome.

The behavioral phenotype of PWS is defined by characteristic pattern of behavior disorder, usually showing rigidity, irritability, labile emotions, impulsiveness, impatience, tendency to confrontation, fabrications, manipulations, tantrums, repetitive behaviors, obsessions/perseverance, lies, self-injury behaviors and anxiety. However, many of these patients find it difficult to express their thoughts, emotions and behaviors due to their inherent intellectual and language delay. In this sense, graphic techniques might be a favorable tool since they rely mainly on a graphic resource, offering significant information for the therapeutic approach.

Methods: This was a non-experimental, descriptive, cross-sectional study. The sample consisted of 25 patients with PWS between 10 and 41 years of age, 15 men and 10 women. All participants receive transdisciplinary treatment at the SPINE Foundation. The projective HTP (house-tree-person) and family techniques were used for the assessment of behavioral trends.

Results: According to the criteria, for the graphic evaluation, established by Emanuel Hammer, Max Pulver y Josep LLuis Font, the following graphic indicators corresponding to the behavioral phenotype were identified: mental rigidity, anxiety, difficulty in adequate externalization and identification of emotions, impulsiveness, aggressive features, poor social skills, need for support and interaction, dependence and lack of empowerment, misfit self-concept, obsessive features, compulsive behaviors.

Conclusions: Graphic tests are intended to evaluate the psychic structure and behavior characteristics in people, and discover emotions or internal conflicts. Any response to a projective material is significant and is considered as an indication of the patient's personality.

In our study, we found that graphical techniques (HPT and Family) are evaluation instruments that can be applied in a population with a mild to moderate intellectual disability, since all the patients correctly understood the task and were able to carry out an adequate production for the evaluation.

It is noteworthy that these graphic techniques provide information in the therapeutic context that, often, works as an invitation to encourage the patient to speak and think about their thoughts, emotions and behaviors. Taking into account that this population has communication difficulties, it provides significant information and reveals conflicts that enable a therapeutic approach and that, otherwise, might not arise. It is important to emphasize that they although also provide convenient information to work with the patient, diagnosis cannot be established upon their basis. Graphic tests can be used as a tool or complement for facilitate the patient means to elaborate their problems and concerns, but it is not advisable to use it them as a single tool for diagnosis.

Poster #51 Effectiveness of Aripiprazole for the Treatment of Prader Willi Syndrome

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Introduction: The behavioral phenotype of subjects with Prader Willi Syndrome (PWS) is characterized by tantrums, stubbornness, oppositional and manipulative behavior, obsessive-compulsive characteristics, emotional lability, aggression, low tolerance to frustration, impatience, impulsiveness, withdrawal, and difficulties in competencies social and interpersonal relationships. Regarding compliance with maturational standards, there is a delay in motor development, language and some degree of cognitive impairment. Psychiatric disorders are frequent in adults with PWS, especially psychosis. Atypical antipsychotic drugs have revolutionized the treatment of schizophrenia and related disorders; being aripiprazole among these. Previous studies suggested that aripiprazole might be a promising treatment of PWS patients with psychosis. However, the FDA has released a warning in this regard among patients at a higher risk of presenting impulse control disorder, who may have uncontrollable desire and behavior while taking aripiprazole. Therefore, the objective of this work was to explore the efficacy of the aripiprazole among patients with PWS who attend transdisciplinary treatment at the SPINE Foundation.

Methods: This is a non-experimental, descriptive, longitudinal design study. The study population comprised individuals with PWS who attend transdisciplinary treatment at the SPINE (Socio-Psycho-Immuno-Neuroendocrinology) Foundation. Final sample was composed of 11 people with PWS, between 10 and 40 years. Half of the patients had previous indication of Aripiprazole, and half of the sample received this pharmacological indication while they assisted to treatment at SPINE Foundation. Aripiprazole is an atypical antipsychotic of third generation that reduces the adverse effects on the metabolism. Most of the patient regularly attended to transdisciplinary treatment at the SPINE Socio-Psycho-Immuno-Neuroendocrinology Foundation.

Results: A total of 11 patients between 10 and 40 years who attend or have attended transdisciplinary treatment at the SPINE foundation, medicated with aripiprazole, showing lack of favorable therapeutic response to this antipsychotic. On the basis of the evaluation of the mental health department of the SPINE Foundation, pharmacological activation effects related to aripiprazole were registered in all patients. The typical behavioral phenotype of subjects with PWS including irritability, opposition, affective lability, impulsiveness, aggressiveness, and low tolerance to frustration, were significantly exacerbated upon treatment onset with aripiprazole. Patients who started at low dosage (1 to 1.5 mg/d) were more irritable, oppositional, labile, promoting crisis. When the dose was increased to 5 mg/d or higher (some patients received up to 20 or 30 mg/d), serious behavioral episodes were documented, including disorganization, aggressiveness, self-injury, impulsivity with behaviors that put the patient's life at risk and home outbreaks. We identified a direct relationship between the medication dose and adverse behaviors.

Conclusions: In this study, aripiprazole was related to exaggerated pharmacological activation effects in subjects with PWS. Further studies are required to confirm this hypothesis in order to improve and anticipate the therapeutic approach of subjects with PWS and their families. Undoubtedly, a transdisciplinary approach was of the utmost importance

in order to be able to assess the behavioral aspects of these patients among the different disciplines involved.

Poster #52 Expressive and Receptive Language Skills in patients with Prader-Willi Syndrome that assist to a Transdisciplinary Treatment in SPINE Foundation

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Introduction: Individuals with Prader Willi Syndrome (PWS) have specific characteristics such as muscular hypotonia, short height, hypogonadism, intellectual disability, psychomotor delay, behavioral and psychiatric difficulties. Regarding the difficulties related to speech and language manifestations, these individuals can show alterations in speech articulation, hyper or hyponasality, and limitations in receptive, expressive language and pragmatic abilities. We aim to describe the linguistic profile of people with PWS, in particular of expressive and receptive language, and its relationship with the verbal intelligence quotient (VIQ).

Methods: We carried on a non-experimental, descriptive, cross-sectional study. All participants regularly attended to a transdisciplinary treatment at the SPINE Foundation. The treatment consist on a comprehensive social-psicho-immuno-neuro-endocrinology approach. Clinical Evaluation of Language Fundamentals-4 (CELF-4) was used to assess linguistic profile involving semantic, morphology, syntactic and pragmatic aspects.

Results: The sample consisted on 12 individuals with SPW between 11 and 45 years old, without growth hormone therapy. Principals results showed a more favourable performance regarding word definitions (5.0 ± 2.5), number repetition (4.5 ± 3.5) and formulated sentences (3.8 ± 2.0). On the other hand, a worse performance was found in understanding spoken paragraphs (2.4 ± 4.5), recalling sentences (2.8 ± 1.8) and word classes total (2.9 ± 2.3). When evaluating the relationship between the CELF 4 subtests and VIQ, we only identified a significant relationship regarding the working memory subtest ($r: 0.73, p= 0.01$).

Table 1. CELF-4 scores

CELF-4 subtest	Score (mean±SD)
Recalling sentences	2.83±1.8
Formulated sentences	3.83±2.1
Word Classes Receptive	2.67±2.6
Word Classes Expresive	3.58±2.3
Word Classes Total	2.92±2.3
Word definitions	5.09±2.5
Understanding spoken paragraphs	2.42±4.3
Number repetition total	4.5±3.6
Familiar sequences 1Y2	3.92±3.8

Table 2. Relationship between CELF-4 and the verbal intelligence quotient (VIQ).

Domain	Spearman's correlation (Rho)	p value
Core Language Score	0.38	0.25
Receptive Language	0.14	0.67
Expressive Language	0.01	0.99
Language content	0.39	0.23
Language memory	0.27	0.42
Working memory	0.73	0.01

Conclusions: In this study, the language profile of patient with PWS showed a better performance on expressive language skills, compared to comprehensive skills. We also identified an association between the VIQ and working memory. Considering the complexity of these patients, It would be necessary for future studies to focus on pragmatic skills, speech, voice, and stomatognathic aspects.

Poster #53 Psychological adaptation and mental health in mothers of people with Prader Willi Syndrome

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Introduction: People diagnosed with Prader Willi Syndrome (PWS) require special care that is psychically and emotionally demanding. Mothers are usually the main caregivers of their children, meaning they may present difficulties adapting to the new situation. Being a caregiver could also be a risk factor for their mental health. There are few studies that focus on the mothers of people diagnosed with a disease. This study aims to evaluate the psychological adaptation and mental health of mothers of people with PWS.

Methods: The study has a non-experimental quantitative design, with a descriptive and cross-sectional scope. The sample consisted of 23 mothers with children with SPW between 1 and 35 years of age. The protocol consisted of a sociodemographic data questionnaire, the Psychological Adaptation Scale (PAS) instrument, which values greater than 3 represent an adequate adaptation, and the Adult Self Report (ASR) questionnaire, which includes a total score of problems in the mental health.

Results: Mothers of people with PWS have an average of 49.86 (SD=25.13) in the mental health problems scale. Regarding the levels of psychological adaptation, the total levels were 4.16. Concerning the different dimensions that compose psychological adaptation, an average of 4.04 was obtained for effective coping; self-esteem with an average of 4.22; spiritual or existential well-being with an average of 4.01; and, finally, social integration with an average of 4.39.

Conclusions: The mental health of the mothers of people with PWS seems to be affected, presenting problem levels (M = 49.86) much higher than the Argentine adults of the general population (M = 40.83) and resembling more the clinical population (M = 55.60), that is, those adults who are starting a therapeutic process.

Regarding the psychological adaptation levels, results show high levels in all of its dimensions. In other words, despite the overload and stress that caring for people with PWS represents, mothers are able to adapt psychologically to the disease.

Poster #54 Personalized learning profile in Prader Willi Syndrome

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Introduction: The present study aims to assess the usefulness of a self-designed tool to identify strengths and weaknesses of cognitive characteristics in people with Prader Willi Syndrome (PWS).

People with PWS are characterized by intellectual disabilities, learning disorders and behavioral problems, demanding specific therapeutic interventions throughout different stages of their lives. The extent of cognitive deficit can be variable, usually mild to moderate. The gold-standard for measure this are Wechsler scales of intelligence (Wais and Wisc III), however, most patient with PWS have very low scores in the scale because concrete thinking and poor interpretation of tasks. For this reason, we start developing an instrument that allows defining a personalized learning profile (PLP). This instrument is being tested in our patients to deepen knowledge regarding impairment of functions related to reading, writing, spatial temporal organization, management and recognition of emotions, visal-motor coordination and numerical calculation; regardless of age.

Methods: This was a non-experimental, descriptive, cross-sectional study. The sample comprised 21 individuals with PWS, males and female, between 10 to 40 years, who regularly attend transdisciplinary treatment at the SPINE Foundation. In order to identify strengths and weaknesses in the cognitive profile, participants were evaluated using the Wisc-III and Wais-III scales, as well as a novel instrument designed in our institution, for defining a personalized learning profile (PLP).

This PLP is obtained from a series of activities to evaluate time-spatial organization, writing, reading, numbering, quantity notions, visual-motor coordination, text comprehension, and recognition of emotions. Each activity is classified as accomplished, in process, or not achieved; and classified into levels (1-3), allowing the therapist to establish goals for treatment and measure progress in the patient.

Results: According to the results of the Wisc-III and Wais-III scales, 10 patients showed strengths in the verbal scale (VS) and 10 patients in the execution scale (ES), and only one case did not present variation between scales. Whereas according to the data obtained with PLP, most patients presented strengths in the recognition of letters, numbers, and basic spatial notions and weakness in the comprehension of texts, additions and subtractions of tens, hundreds without concrete support. Most patients were able to complete level 1, but only few cases managed to complete levels 2 and 3.

Conclusions: We found out in our study that Wechsler scales can be usefully complement with PLP. The main cognitive difficulties found comprised failure in the sequential processing of information, working memory, logical-mathematical reasoning, accepting or understanding a point of view different from theirs, auditory verbal processing, attention, concentration, writing and executive functions. While the main strengths identified involved long-term memory and perceptual organization. This mixed information would be very useful to design specific intervention strategies aimed at the rehabilitation of the impaired cognitive abilities.

Poster #55 Visual-motor integration in Prader Willi Syndrome without growth hormone

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Introduction: The present work aims to describe visual motor integration characteristics in people with Prader Willi Syndrome (PWS) without growth hormone. Within the clinical characteristics that are relevant for Occupational Therapy approach, patient with PWS has deficiencies in vision, fine and gross motor coordination, psychomotor development, sensory integration and learning, as well as intellectual disability and hypotonia.

Methods: A total of 17 people with a diagnosis of PWS between 13 and 39 years old, 64.7% males and 35.3% females, participated in the study. Another 10 cases must have been excluded from the study due to the irregularity with which they attend to treatment at the SPINE foundation, due to the taking of growth hormone or due to comorbidity with an autism spectrum disorder. The Beery-Buktenica Developmental Test of Visual-Motor Integration test (Beery VMI) was used. It was administered individually the complete form of the test consisting of 3 subtests. This instrument was designed by its authors to identify significant difficulties in visual motor integration, visual perception and motor coordination.

Results: The Beery VMI results showed that all the participants are in the Very Low category in the Visual-motor Integration subscale and in the Motor Coordination subscale. In the Visual Perception subscale, better results are seen, 88.2% obtained a Very Low score, a 5.9% Low score and a 5.9% Average score. When analyzing the scores of each section, it is observed that the highest values were found in the area that evaluates Visual Perception (53.73 ± 13.56), revealing a lower score in the area of Motor Coordination (47.35 ± 6.13) and Visual-motor Integration (48.94 ± 7.94).

Conclusions: According to the results obtained through the Beery VMI test, we can conclude that people with PWS without growth hormone, both adolescents and adults, show a better performance in visual perception, even though they are below the expected results for their different ages. In terms of motor coordination, their scores are even lower, also interfering with the Visual-motor Integration, since motor coordination and visual perception are the skills that influence their visual-motor integration performance. It is argued that with a regular and specific intervention in visual motor integration, patients with PWS could improve their test results. At a certain point they will also be able to maintain and not worsen such skills.

Poster #56 Identifying relevant rehabilitation goals for cognitive training in adults with Prader-Willi Syndrome

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Introduction: Although focusing on patients' identified personal goals is essential during rehabilitation, it can be challenging to choose relevant and realistic goals in patients with cognitive impairment. In Prader-Willi Syndrome (PWS), metacognitive difficulties lead to a lack of awareness of patients regarding their cognitive deficits that impact the choice of relevant rehabilitation goals. A method for choosing and evaluating a rehabilitation effect on personalized goals is Goal Attainment Scaling (GAS). Our aim was to explore the feasibility of using GAS for goals related to planning difficulties in patients with PWS during rehabilitation training.

Methods: In order to identify patients' planning difficulties as part of the ETAPP study (Evaluation of a Therapeutic Aid of the Planning function in Prader-Willi Syndrome), we designed a multi-steps approach involving firstly the patient's primary caregivers who filled in the Dysexecutive Questionnaire from the Behavioural Assessment of the Dysexecutive Syndrome and the 6-Item version of the Disability Assessment for Dementia. These questionnaires provided a basis for a phone-interview by a psychologist with the patient's caregivers regarding planning difficulties and allowed to evaluate the patient's executive difficulties in his/her ecological context. A face-to-face interview was then conducted by an occupational therapist (OT) with the patient him/herself using the report of the phone-interview with caregivers to lead the discussion. Comparison of those two interviews provided information about differences in perceived difficulties and priorities between the patient or his/her caregivers, as well as an indication of the patient's insight of his/her difficulties. Following the interview of the OT with the patient, personalized goals were selected and transformed into GAS. Two external judges scored GAS quality on SMART criterion extended. After the final training session, GAS were rated by the OT that conducted the intervention and by the patient.

Results: All goals could be set within the activity and participation domains of the International Classification of Functioning Disability and Health. Most goals were related to learning new strategies or using devices/support (charts, diary...) and included for example organising holidays, preparing a suitcase, using diary for key events, laundry management, attending leisure activity. Quality of GAS was found to very good (mean = 2.75/3). Results indicated that relevant goals for patients with PWS can be far from what caregivers and rehabilitation staff think of important issues. This gap can be the origin of situations causing important frustration and a lack of motivation for the patient and could explain the weakness of efficiency of some rehabilitation training. Results also showed that 65.2% of the patients considered that they had achieved their rehabilitation goals (scores from 0 to +2) versus 43.4% according to OT.

Conclusions: Using GAS for goals related to planning difficulties in patients with PWS appeared to be feasible and useful to focus on patient's relevant goals during rehabilitation. Implication of patient's caregivers is also essential to explore difficulties in patient's ecological context and improve adaptation in their life.

Poster #57 Feasibility and effectiveness of a metacognitive training of planning abilities in adults with Prader-Willi Syndrome

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Introduction: Deficits in executive functions and intellectual disability are well documented in Prader-Willi Syndrome (PWS) and result in daily life difficulties and poor personal autonomy of patients. Difficulties in planning are particularly disabling for everyday actions like being able to plan an appointment and be there on time, being able to take the bus independently... One of the purposes of cognitive rehabilitation is to target and minimize disabled functions in patients. In executive dysfunction, metacognitive strategies are recommended because of a step-by-step approach which simplifies learning. For example Goal Management Training (GMT) helps individuals to efficiently encode goals in order to achieve a task by learning a mental checklist routine to maintain focus on the task. The aim of this study is to explore the feasibility and the effectiveness of a metacognitive strategy training on daily life planning difficulties in adults with PWS.

Methods: The ETAPP program (Evaluation of a Therapeutic Aid of the Planning function in Prader-Willi Syndrome) is a composite cognitive rehabilitation method based on GMT and others metacognitive strategies (auto-regulation scripts, problem-orientation...), consisting in six sessions of rehabilitation. With a double-blinded two-group randomized controlled trial, we compared planning performance of patients undergoing the cognitive training focusing on planning with those of a control group receiving usual care. Because focusing rehabilitation on patients' identified personal goals improves motivation and therapeutic alliance, daily life planning difficulties were identified and transformed into measurable goals using Goal Attainment Scaling (GAS). The main outcome was the performance on the Modified Six Elements (MSET) subtest from the Behavioural Assessment of Dysexecutive Syndrome. Patients were also evaluated on three executive tasks to assess updating, shifting and inhibition. In order to monitor punctuality and anticipation of actions, patients had to complete between-session assignments throughout the study.

Results: Over the course of eighteen months, we included 27 participants in the experimental group and 26 in the control group during their stay in the French Reference Center for PWS in Hendaye (France). Results show improvement of performances in the MSET and the others measures but no difference between the two groups. Both groups showed improvement on personalized goals measured with GAS (62.5% vs. 68.1%).

Conclusions: Quantitative data do not allow us to conclude to an effect of the cognitive remediation on executive functions but more qualitative data remind us the importance of personalized goal in rehabilitation and the variability of performance regarding intellectual disability. Considering the small number of sessions imposed by the length of their stay in the rehabilitation unit, a second study of the ETAPP program should be considered to explore the benefit of a more intensive training.

Poster #58 Presentation of the PRACOM (PRAdler Willi COMMunication) project

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Background: The Prader Willi Syndrome (PWS) is a rare and complex, genetic disease characterized by a slight intellectual delay to moderate with obesity problems and disorders behaviors that can impede social relationships. The incidence is 1 birth on 25 000. The different manifestations of the syndrome result in social and professional integration difficulties (only 4% of adults PW in France live alone). The insertion in the community or in helping families daily by labor and management is difficult due to very frequent behavior disorders, for example, more than 80% of patients SPW are tantrums. However, at the present time, reasons related to these disorders are unknown.

Relevance of the research: In view to the difficulties of patients both academic and professional, and the impact of the disorders on families and caregivers (stress, burden...), the identification of factors explaining these disorders would allow a better understanding of the syndrome as a whole and a better adaptation of the care. Furthermore, the proposal of new therapies is a major issue in this syndrome for which there is today no medical treatment.

Objectives: The PRACOM (PRAdler Willi COMMunication) project is to identify and characterize disorders emotional functioning including those related to anger and their consequences at the behavioral level, to situate them in their contexts environmental (frequency, cause, consequences on the well-being and parental, school or professional relationships) and propose innovative therapeutic avenues to improve these behavioral disorders.

Methods: Different questionnaires, neuropsychological tests, cognitive tasks and structured interviews will be administered to 30 children and 30 adults with PWS, 30 children and 30 adults control (without pathology), their parents and care professionals caregivers. At the end of these assessments, 3 therapies will be proposed to some patients with behavioral disruption: 1) a psycho-social program of emotional regulation, 2) a program of transcranial stimulation for adults with PWS, and 3) a program of external stimulation of the vagus nerve for children with PWS.

Expected results: A better understanding of the factors related to temper tantrums will improve management of patients SPW into their families and institutions and new therapeutic avenues may be proposed according to the relevance of the effects observed and extended to pathologies and similar disorders.

Poster #59 Evaluation of a specialist mental health / behavioural service for young people with PWS

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Introduction: Children and young people with PWS are susceptible to comorbid mental health and behavioural problems and benefit from an early intervention to reduce disruption in their family lives and educational placements. National and Specialist CAMHS Learning Disabilities team at the Maudsley Hospital in London provides specialist behavioural interventions for young people with PWS, behaviour management advice to their families and carers, and multiagency liaison with local services. The results demonstrate effectiveness of the interventions offered by the Learning Disability Team in prevention and management of behaviour disorders and mental health problems in children and young people with PWS.

Methods: A short answer questionnaire was sent to twenty-two families who attended the service over the past 5 years in order to understand the effectiveness of the provided interventions and improvements in parental knowledge and understanding of behaviour problems associated with PWS.

Results: Feedback from the satisfaction survey indicated that 85% of families felt that their understanding and management of PWS and the comorbid mental health and behavioural problems had improved and over 70% of the families would recommend the service. A matched-paired t-test of the outcome measure used by the service, Children's Global Assessment Scale, showed a significant increase in scores from referral to discharge suggesting an overall improvement in functioning.

Conclusions: The results demonstrate effectiveness of the interventions offered by the Learning Disability Team in prevention and management of behaviour disorders and mental health problems in children and young people with PWS.

Poster #60 Clinical and electrophysiological markers of genetic high-risk for psychosis in Prader-Willi Syndrome

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Introduction: PWS is a rare genetic disease with a characteristic physical and behavioural phenotype resulting from the lack of paternal expression of maternally imprinted genes at 15q11-q15. This is mainly due to a paternal deletion of this region (delPWS) or a maternal uniparental disomy (mUPD). While people with PWS all share common symptoms, only those with the mUPD genetic sub-type are at very high risk for psychotic illness (up to 60% in adults with mUPD). This increased risk of developing psychosis in mUPD has been hypothesised to be due to the over-expression of maternally expressed genes, which many have the potential to disturb the GABA/glutamate equilibrium, that has been shown to account to psychotic symptoms. However, very little research has been conducted to explore this hypothesis.

We are undertaking a case controlled study investigating markers of genetic high risk for psychosis in PWS using clinical, electrophysiological (EEG), psychiatric, neuroimaging (MRS), and cognitive measures. This study will determine whether these markers differ according to genetic subtypes of PWS and/or the presence of psychopathology. If they do, they might explain mechanisms of psychosis in PWS. The results of a pilot study investigating feasibility and acceptability of the methodology and the findings from adults with PWS in the pilot study with different genetic types will be presented.

Methods: Participants with the two main genetic types of PWS and also typically developing age and gender matched sibling controls will come for 2 days to the research centre in Cambridge, UK. The relationships between age, genetic type, psychopathology and EEG and MRS measures will be explored. The study will be divided into 5 parts:

- EEG assessment: Measures of P50 sensory gating, mismatch negativity (MMN), and subsequent P300 responses will be conducted.
- Neuroimaging: volunteering participants will undergo a structural MRI followed by the acquisition of GABA levels in the ACC and the temporal lobe using MRS.
- Cognitive assessments: IQ (WASI), processing speed (Trail-making test), working memory (subscales of the WAIS), and sensory processing (The Sensory Perception Quotient) will be measured.
- Psychiatric assessments: measures of schizotypy (O-LIFE), prodromal symptoms of psychosis (CAARMS), anxiety, and depression (Glasgow Depression Scale and Glasgow Anxiety Scale) will be conducted. A more general psychiatric screening using the MINI-PASSADD will also be conducted.

Conclusion: This study is a unique opportunity to investigate electrophysiological markers of psychosis, cognition and proxy measures of brain GABA metabolism in PWS. The long term aim is to identify potential causative mechanisms for psychosis and inform treatment.

Poster #61 I am bilingual, I am proud... and I am good! Code-switching as a tool to determine the status of grammatical gender in the grammar of a PWS English-Spanish bilingual

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Introduction: Relatively extensive research has been conducted on the intellectual disabilities, behavioural disturbances and cognitive capacities of individuals with PWS. This contrasts with the fact that their language development remains almost entirely unexplored and limited to the speech and voice characteristics and the narrative abilities in monolingual individuals. To overcome this scarcity, we have set a program intended to investigate the linguistic abilities of this population. In this study we have used code-switched structures to investigate how grammatical gender is represented in the mind of a 34 year old adult male English-dominant English-Spanish bilingual (Spanish is the Heritage language) with PWS. Previous research has shown that typically-developing (TD) Spanish-dominant English-Spanish bilinguals prefer gender-matching switched Determiner+Noun (concord) and Subject+Adjectival Predicate (agreement) structures, as (1a) versus (1b) over non-matching ones, as (2a) versus (2b), which means that these bilinguals abide by the so-called 'analogical criterion (AC)': they assign English Nouns the gender of their translation equivalent in Spanish. For their part, English-dominant English-Spanish bilinguals are less consistent with their preference for the AC, as their ratings for matching items and their supplying matching articles and adjectives depends on the type of structure and on the experimental task (Licerias et al. 2016; 2017).

Methods: In order to determine whether this English-Spanish bilingual with PWS behaved like English-dominant TD English-Spanish bilinguals he was administered an *Acceptability Judgment Task (AJT)* and a *Sentence Completion Task (SCT)*. In the AJT he rated 12 switched concord and 12 switched agreement structures (conditions 1 and 2) on a Likert scale numbered from 1 to 4, 1 being very bad and 4 being excellent. Six items were masculine and 6 were feminine (3 items were matching and 3 were non-matching).

(1a) Concord SP-EN matching: (el_{the-masc} sun_{sol-masc})

(1b) Agreement SP-EN matching: (the building_{edificio-masc} es rojo_{red-masc})

(2a) Concord SP-EN non-matching: (la_{the-fem.} sun_{sol-masc})

(2b) Agreement SP-EN non-matching: (the building_{edificio-masc} es roja_{red-fem.})

In the SCT, he had to complete code-switched sentences by writing the Spanish determiner (concord) in 20 items as in (3) or the Spanish colour adjective (Agreement) in 20 items as in (4).

(3) Concord: [(__el/la__ book_{libro-M})]

(4) Agreement: [(the book_{libro-M} es rojo_{-M}/roja_{-F})]

Results: In the AJT he exhibits a high degree of acceptance for both matching and non-matching structures, although he has a stronger preference for the concord and the agreement structures that abide by AC, as he gives a higher rating to the matching structures in (1) than to the non-matching ones in (2). In the SCT he systematically abided by the AC when producing the two types of structures, thus performing at ceiling in both concord and agreement, as TD Spanish-dominant bilinguals do (Valenzuela et al. 2012; Fernandez & Licerias, 2018).

Conclusions: The fact that our PWS participant performs at ceiling in SCT and prefers between matching to non-matching code-switched concord and agreement structures in the AJT evidences that the representation of the gender features in his mind mirrors that of the Spanish-dominant TD bilinguals, and is therefore consistent with the position that parents should be supported in their decision to provide bilingual input to their children with PWS, since in this case and even though he is not Spanish dominant, he behaves like one when dealing with gender representation and processing.

Poster #62 Application of PQIF for behavioral management in Prader-Willi syndrome

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Introduction: Parent orientation programs are conducted in order to train parents to better manage their children's behaviors. However, although there are researches that aim to develop and evaluate the effectiveness of programs, there is a shortage of programs that are specialized in patients with psychiatric or developmental clinical diagnoses. Therefore, this study aimed to evaluate the application of the Family Interaction Quality Program (PQIF) to parents of children with Prader-Willi syndrome, including the adaptations necessary to address the specific characteristics of the syndrome.

Methods: The group had seven participants who were parents of children up to the age of eight years with Prader-Willi syndrome who were invited to participate during the medical consultation at the pediatric endocrinology clinic of the Hospital das Clínicas of São Paulo. There were nine weekly meetings lasting two hours each. The program includes a previous group meeting to present the proposal, signing a consent form and applying measurement instruments, which were also applied at the last meeting. They are: Questionnaire on Prader-Willi syndrome, Parental Styles Inventory (PSI), Functional evaluation of problem solving.

Results: The parental style score demonstrated an increase in the use of positive parental practices for 6 of the 7 participants, and better observation and discrimination of the behaviors themselves. In addition, it was possible to observe an expansion in the repertoire of behavioral analysis - own and their children - and of appropriate management - affectionate dialogue, presentation of clear, coherent and consistent rules and avoidance of punishment.

Conclusion: The results indicate that PQIF is an important tool to assist the parents of children, including in the context of special needs such as Prader Willi Syndrome, and the management of behaviors in order to promote quality in family interaction.

Poster #63 Investigating the Allocation of Visual Attention to Salient Stimuli in Infants and Young Children with Prader-Willi Syndrome

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Introduction: The characteristics of Prader-Willi syndrome (PWS) include food preoccupation, and impairments in social functioning. Difficulties develop throughout early childhood, becoming more evident in adolescence and adulthood. Specific difficulties lie in the recognising and processing of visual social cues and an inability to effectively interpret social situations. In addition, individuals with PWS develop an insatiable appetite, with young children with PWS reported as demonstrating difficulties in shifting attention away from food, which might further impact on social functioning. The present study aims to 1) investigate if the allocation of attention towards visually-salient stimuli; emotional stimuli, and food stimuli in infants and children with PWS, differs from chronologically and social developmentally-matched typically developing children and 2) examine if infants and children with PWS show an attentional bias toward food stimuli relative to equi-salient visual or emotional stimuli, compared to typically developing children. This study aims to produce research that contributes to the progression and development of early stage preventative treatments, and also inform the use and development of other therapeutic strategies, such as intranasal oxytocin and agents that act on the feeding pathways of the brain.

Methods: Three groups of children will participate in the study: 15 children with PWS (N=15) aged between 12 and 30 months, 15 age-matched typically-developing children and 15 social developmentally-matched typically-developing children. A preferential looking paradigm will be used to assess infants' relative attentional allocation toward salience-graded emotional, food and (perceptually-matched) visual object stimuli. We hypothesise that PWS children will be disproportionately biased towards food stimuli over neutral or emotional stimuli.

Established questionnaires, including the Communicative Development Inventory, and ASQ-SE will be employed to assess early social, emotional and language development. The Early Social Communication Scales will provide measures of individual differences in nonverbal communication skills, and allow us to social developmentally-match the PWS participants to typically-developing children. The Dykens et al. (2007) 13-item Hyperphagia Questionnaire will be administered to assess food interest in infants and children with PWS, and our Background Questionnaire will assess family background; pregnancy and delivery, dietary information, genetic diagnosis, and general health.

Results: To date, of the proposed 45 participants, 7 PWS infants and 9 typically-developing children have been assessed. I will present the findings from our measures of social development and the preferential looking paradigm, and discuss any group differences between PWS and typically-developing children. Presently, our data suggests that there may be differences in the allocation of visual attention to stimuli, as well as nonverbal communication skills, and language.

Poster #64 Importance of early stimulation and follow up of neurodevelopment in patients with Prader Willi syndrome. Our experience in Cardenas city.

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Introduction: Prader Willi syndrome (PWS) is a rare genetic disease, characterized by anomalies of the hypothalamus-hypophysis axis. It presents with profound hypotonia, starting in the neonatal period, mainly the first two years of life, hyperphagia with high tendency to develop morbid obesity in childhood and adulthood, learning difficulties and grave behavioral and/or psychiatric disturbances.

Methods: an observational study was carried out to four children with signs of presumptive PWS that were admitted in their first month of life at the neurodevelopment clinic of Cardenas city with the aim to set guidelines for early diagnose and assessment, through a multidisciplinary approach by a professional team composed of Clinical Geneticist, Genetic Counselor, Neonatologist, Neuropediatrician and Physiotherapists, with the aim to set guidelines for the assessment and early diagnosis of conditions resembling PWS. Early stimulation of neuromotor skills was started in a joint effort with the family along with a systematic assessment of their neurodevelopmental stages.

Results: the four patients, showed a severe hypotonia in the neonatal stage and delay in their psychomotor functions. Care and follow up showed an evident improvement of the neuromotor and language skills following physiotherapy and phoniatic therapies. A higher involvement of the family was achieved, upgrading their knowledge and acceptance of the condition.

Conclusions: with early stimulation and multidisciplinary follow up of patients with PWS a noticeable improvement of their psychomotor development and quality of life.

Poster #65 Influences of Social Cognition and Reward Processing on Autism Symptoms in Prader-Willi Syndrome

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Introduction: Prader-Willi Syndrome (PWS) is a neurogenetic syndrome caused by the loss of expression of paternally expressed genes from the paternally inherited copy of chr15q11-13 (Bittel et al., 2005). PWS is characterised by the onset of hyperphagia in childhood leading to morbid obesity. Hyperphagia in PWS is considered to be due to an impaired satiety response and an increased reward value of food. Autism Spectrum disorder (ASD) symptoms, including atypical social cognition, are prevalent in PWS cases and intriguingly, appear to increase in PWS across childhood (Bennet et al., 2015). The social motivation theory of ASD proposes that social cognition impairments are largely driven by social motivational deficits (Chevallier et al., 2012). We hypothesise that the onset of hyperphagia may reduce the reward value of social stimuli and contribute to the relative increase of ASD symptoms seen in later childhood in PWS cases.

Methods: We will phenotype ASD symptoms and hyperphagic behaviour in individuals with PWS (n=60, age 4-40y) and age matched controls. To test if reduced valence of social reward underpins ASD symptoms in PWS, we will characterise social cognition comprehensively using a battery of accessible and validated eye-tracking paradigms. To test the relationship between reward valence for social cognition and hyperphagia, we will compare reward processing for food stimuli; social stimuli; and non-food/non-social stimuli. A dynamic preferential looking paradigm will be used to investigate differences in attentional bias between PWS cases and controls in hungry and satiated conditions.

Results: Data collection for this study is on-going. We will present preliminary analysis from the initial recruitment phase of performance of PWS cases and controls on the eye-tracking batteries.

Conclusion: The results of this study will help us understand if reduced valence of social reward underpins ASD symptoms in PWS and if it is related to the onset of hyperphagia.

Poster #66 Treatment Experiences of Mental and Behavioral Disorders in Outpatients with Prader-Willi Syndrome in Germany

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Introduction: Prader-Willi Syndrome is a neurodevelopmental disorder with typical clinical manifestations. The most consistent manifestations include hypotonia and poor weight gain in infancy, hypogonadism, early childhood-onset hyperphagia and obesity. Especially during young adulthood behavioral problems and often psychiatric disturbances occur frequently. Mostly tantrums, temper outbursts in combination with self-harm and aggressive behavior lead to problems in everyday life. These situations consequently create the need for psychiatric consultation. Unfortunately most clinical guidelines do not match the psychiatric needs of patients with Prader-Willi Syndrome. Side effects and adverse effects occur more often when using psychiatric treatment guidelines established for patients without Prader-Willi Syndrome. Moreover a variety of medications with antipsychotics, antidepressants and anticonvulsive agents can be seen generating variable response and not only beneficial effects.

Methods: A psychiatric outpatient clinic was established at the Hannover Medical School in 2010 due to the need for psychiatric treatment of patients with Prader-Willi Syndrome. Since then we treated more than 120 patients ages 12 to 55 with Prader-Willi Syndrome, some living at home with their families, most of them living in specialized institutions. Due to the lack of clinical studies concerning the psychiatric treatment of patients with Prader-Willi Syndrome we started a retrospective study to rate and summarize the treatment of typical psychiatric symptoms in patients with Prader-Willi Syndrome.

Results: Results so far indicate that treatment with serotonin reuptake inhibitors (SSRIs) reduces frequency and intensity of temper outbursts and reduces daytime sleepiness. Obsessive-compulsive symptoms decreased in severity. Patients treated with SSRIs presented a more balanced mood, self-harming behavior decreased. Less inpatient treatment was necessary. No significant weight gain was reported but uneasiness and insomnia forced us to cease the medication in some cases. Overall side effects did not occur more often than in general psychiatric patients treated with SSRIs.

Conclusions: SSRIs represent a well-tolerated medication to treat the typical psychiatric symptoms frequently seen in patients with Prader-Willi Syndrome as listed above. As far as our experience goes, SSRIs can be seen as a first line medication in the psychopharmacological treatment of patients with Prader-Willi Syndrome.