intellectual disability, polypharmacy and use of psychotropic drugs. Missed diagnoses were common and many patients had undergone extensive diagnostic tests for symptoms that could actually be explained by their syndrome. Fatigue (52%), abdominal discomfort (23%) and hypertension (10%) were among the most frequent reasons for referral to Internal Medicine. Based on the literature and our clinical findings, 73% of the syndromes was associated with endocrine problems. We provide an algorithm for the clinical approach to CRGS adults, in order to prevent unnecessary diagnostics as well as missed diagnoses.
Conclusion: Our overview of 726 adults with CRGS shows that missed diagnosed and needless invasive tests are common in this patient population. As more and more CRGS patients are now reaching adult age and transfer to Internal Medicine, internists and endocrinologists should be aware of the special needs of adults with CRGS and of the medical pitfalls. Knowledge about syndrome-specific health problems and multidisciplinary expert care is crucial to prevent the personal and financial burden of unnecessary diagnostics and under- and overtreatment.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Young Adult LEW.1WR1 Rats, a Model of Liver FAT10 Overexpression, Develop Insulin Resistance and Fatty Liver With Age

Madushika M. Wimalarathne, PhD student[1], Luis D. Mercado, BS[2], Quiana C. Wilkerson Vidal, MS[3], James Wolfsberger, MS[2], Victoria J. McConnell, MD[2], Bernhard Vogler, PhD[2], Sharifa Tahirah Love-Rutledge, PhD[2].
[1]University of Alabama in Huntsville, Huntsville, AL, USA, [2]University of Alabama at Huntsville, Huntsville, AL, USA, [3]University of Alabama Huntsville, Huntsville, AL, USA.

As human lifespan increases, comorbid conditions that impact quality of life have become a serious problem. FAT10 has been identified as a gene that when knocked out, improves age associated metabolic dysfunctions and increased longevity in mice (1). There is increased *Fat10* expression in the liver in obesity (2,5). Providing evidence that fat10 expression may be important for triggering the transition to metabolic dysfunction in aging. Adult LEW.1WR1(1WR1) rats have increased body mass without excess abdominal fat mass compared to control rats (3). Yet, it was unclear where the excess mass was stored. We hypothesized that the 1WR1 rat would develop increased liver fat mass as a product of increased insulin resistance in response to increased liver fat10 expression over time. To test this hypothesis, we did insulin tolerance tests(7 weeks & 15 weeks), triglyceride assays, and histological analysis of the liver(23 weeks), in 1WR1 rats(n=7) and Wistar Furth (WF) rats(n=7) on control diets. We analyzed images using histological scoring for nonalcoholic fatty liver disease from the literature (4). We also assessed the slides for Mallory Denk bodies (MBs). The body mass of 1WR1 rats were increased compared to WF rat groups starting from the age of 7 weeks (391.4∓8.572g vs. 271.8∓11.62g; p <0.0006). 1WR1 rats became more insulin resistant with age, the 1WR1 rat group has increased AUC of 7 and 15 week Insulin Tolerance Tests (401.5∓23.54 vs. 245.3∓10.20 7w ITT1; p= 0.0728, 15w ITT2 328.2∓14.86 vs. 217.8∓9.; p <0.0003) compared to WF rats. 1WR1 rats have increased liver mass (11.85g∓0.7699g vs. 7.235g∓0.3864g; p=0.0006) liver triglyceride levels compared to WF rats (192.8∓21.8 mg/mL vs. 130.1∓13.075 mg/mL; p=0.0728). 1WR1 rats have increased steatosis scores(1.857∓0.2608 vs. 1.143∓0.1429;p= 0.0862) yet significantly reduced inflammatory foci level (2∓0.8165 vs. 3∓0;p= 0.007), most 1WR1 hepatocytes are enlarged (ballooned) and contained MBs compared to WF rats suggesting 1WR1 rats have already passed the early inflammation stage. Adult 1WR1 rats developed reduced insulin sensitivity and lipid accumulation in the liver. These data support our hypothesis that 1WR1 rats would develop increased liver fat and impaired insulin resistance in response to aging and show that this process may be inflammation driven.
(1) Canaan et al.,PNAS. April 2014; 111 (14): 5313-5318.**(2)**Vidal et al., FASEB.2020, 34: 1-1,**(3)** Collins et al., J Endocr Soc. 2019;3(1),**(4)**.Kleiner et al., Hepatology, 2005; 41 (6): 1313–1321,**(5)**.Dali-Youcef et al., Hepatol Commun. 2019;3(9):1205-1220.

Neuroendocrinology and Pituitary

CLINICAL ADVANCES IN PITUITARY DISEASES

GLP1 Receptor Agonists Reduce Fluid Intake in Primary Polydipsia

Bettina Felicitas Winzeler, MD[1], Clara Odilia Sailer, PhD[1], David Coynel, PhD[1], Vogt Deborah, PhD[1], Zanchi Davide, PhD[1], Sandrine Urwyler, MD[2], Julie Refardt, MD[3], Mirjam Christ-Crain, Prof[4].
[1]University of Basel, Basel, Switzerland, [2]University Hospital Basel, Rheinfelden, Switzerland, [3]Erasmus MC, Rotterdam, Netherlands, [4]Universitaetsspital Basel, Basel, Switzerland.

Background Primary polydipsia, characterized by excessive fluid intake, carries the risk of water intoxication and hyponatremia, but treatment options are scarce. Glucagon-like peptide-1 (GLP-1) reduces appetite and food intake. In experimental models, they also play a role in thirst and drinking behavior in. The aim of this trial was to investigate whether GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia. **Methods:** In this randomized, double-blind, placebo-controlled, 3-week crossover-trial, 34 patients with primary polydipsia received weekly dulaglutide (Trulicity®) 1.5mg and placebo (0.9% sodium chloride). During the last treatment week, patients attended an 8-hour evaluation visit with free water access. The primary endpoint was total fluid intake during the evaluation visits. The treatment effect was estimated using a linear mixed-effects model. In a subset of 15 patients and matched controls, thirst perception and neuronal activity in response to beverage pictures were assessed by functional MRI. **Results** Median [IQR] total fluid intake was 2250ml [1600-2600] on dulaglutide versus 2400ml [1850-3400] on placebo. Patients on dulaglutide reduced fluid intake by 490ml [95%-CI -780, -199], p=0.002, corresponding to a relative reduction of 17%. 24-hour urinary output was reduced by -943ml [95%-CI -1473, -413]. Thirst perception in response to beverage pictures

was higher in patients with primary polydipsia versus controls and lower on dulaglutide versus placebo, but functional neuronal activity was similar between groups and treatments. **Conclusion:** GLP-1 receptor agonists reduce fluid intake and thirst perception in patients with primary polydipsia and could therefore be a novel treatment option for these patients.

Neuroendocrinology and Pituitary
CLINICAL ADVANCES IN PITUITARY DISEASES

Metyrapone Treatment in Endogenous Cushing's Syndrome: Results at Week 12 From PROMPT, a Prospective International Multicenter, Open-Label, Phase III/IV Study

Lynnette K. Nieman, MD[1], Marco Boscaro, MD[2], Carla Maria Scaroni, MD[2], Timo Deutschbein, MD[3], Emese Mezosi, MD[4], Natacha Driessens, MD[5], Carmen Emanuela Georgescu, MD[6], Alicja Hubalewska-D, Prof[7], Dilek Berker, MD[8], Barbara Maria Jarzab, MD, PhD[9], Dominique M. Maiter, MD, PhD[10], Martin Reincke, MD[11], Paola Loli, MD[12], Benedetta Zampetti, MD[13], Ayşegül Atmaca, MD[14], Corin P. Badiu, MD, PhD[15], Albert M. Beckers, DSC, MD, PhD[16], Marek Bolanowski, PhD, MD[17], Francesco Cavagnini, MD[18], Nicole Unger, MD[19], Roberta Giordano, MD, PhD[20], Felicia Alexandra Hanzu, MD, PhD[21], Massimo Terzolo, MD[22], Martine Bostnavaron, MD[23], Miklos Toth, MD, PhD, DSci[24].

[1]National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD, USA, [2]Endocrinology department, University Hospital, Padova, Italy, [3]Dept. of Internal Medicine, Div. of Endocrinology and Diabetes, University Hospital, University of Würzburg, Wurzburg, Germany, [4]Department of Internal Medicine, University Medical School, Pecs, Hungary, [5]CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium, [6]Dept of Endocrinology, Cluj County Emergency Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania, [7]Chair and Department of Endocrinology, Jagiellonian University, Medical College, Krakow, Poland, [8]Endocrinology department, Numune Training and Research Hospital, Ankara, Turkey, [9]Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland, [10]Endocrinology department, University Hospital Saint Luc, Brussels, Belgium, [11]Endocrinology department, University Clinic, Munich, Germany, [12]Clinica San Carlo, Endocrinology department, Milan, Italy, [13]Niguarda Hospital, Endocrinology department, Milan, Italy, [14]Endocrinology department, Ondokuz Mayıs University, Samsun, Turkey, [15]"C.I Parhon", National Institute of Endocrinology, University of Medicine and Pharmacy, Bucharest, Romania, [16]Endocrinology department, University Hospital, Liege, Belgium, [17]Dept. of Endocrinology, Diabetes and Isotope Therapy, Medical University, Wroclaw, Poland, [18]Endocrinology and Metabolism department, Hospital San Luca, Milan, Italy, [19]Department of Endocrinology and Metabolism, University Hospital, Essen, Germany, [20]Endocrinology department, University of Turin, Turin, Italy, [21]Endocrinology department, Hospital Clinic, Barcelona, Spain, [22]Dept. of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, Orbassano, Italy, [23]HRA-Pharma Rare Diseases, Paris, France, [24]Semmelweis University, Department of Internal Medicine and Oncology, Budapest, Hungary.

Background: Metyrapone is a steroidogenesis inhibitor approved in Europe for the treatment of endogenous Cushing's syndrome (CS) based on observational retrospective studies published over more than 50 years. We present data from the first prospective study designed to confirm metyrapone efficacy and good tolerance in patients with CS.
Methods: This single arm, open-label, multicenter, international trial enrolled 50 patients with CS who had three baseline 24 hours urine free cortisol (UFC) values at least 50% above the upper limit of normal (ULN=165 nmol/24h). Metyrapone was titrated over 12 weeks (W12) to achieve normal urine (mean of 3 values, mUFC) and serum cortisol levels. Patients whose mUFC did not exceed 2-fold the ULN could enter a 6-month extension period. The primary efficacy endpoint was the proportion of patients with mUFC ≤ ULN at W12 assessed in a central laboratory using LC-MS/MS. The most important secondary endpoint was mUFC decrease of ≥ 50% at W12.
Results: At baseline: mean age was 47 years, median mUFC (range) was 570 (291 - 8476) nmol/24h (3.5 x ULN). Hypercortisolism was in 96% of patients either moderate (mUFC ≥ 2xULN; < 5x ULN) in 63% or severe (≥5 x ULN) in 33%. Hypertension (69%) and diabetes mellitus (47%) were the most common comorbidities. At W12: 47% (23/ 49) met primary endpoint. Another 40% (19 / 49) had mUFC ≤ 2xULN. Median percentage decrease in mUFC from baseline to W12 was -74%. Secondary endpoint was met by 80% of patients who had a mUFC decrease of 50%. Final median metyrapone dose was 1500 (250; 5500) mg/day. Physical signs and symptoms were normalized or improved in 66% of patients. Circulating cholesterol, HbA1C and fasting glucose and insulin improved with median decrease of 12%, 3%, 5% and 9% respectively and median systolic and diastolic blood pressure also decreased by 4 and 5mmHg respectively. Among patients with antihypertensive treatments, 10 (31%) had a decrease in number of drugs and 5 (16%) had an increase in number of drugs during the study. Median ACTH increased by 11 % from baseline.
Twenty six (52%) patients experienced mild to moderate study drug related adverse events (AEs). One patient discontinued before W12 because of an unrelated SAE on day 2 (pneumonia with septic shock). The most common AEs were nausea (24%), decreased appetite (18%), fatigue (14%), headache (10%), peripheral edema (6.0%), hypokalemia (6.0%) and hypertension (6.0%). Reversible adrenal insufficiency occurred in 6 (12%) patients. Few patients 14% (7/50) experienced at least one AE that led to a dose interruption or dose adjustment. Cushing Quality of Life Questionnaire increased of 10 points from baseline which is close to minimal clinically important difference = 10.1. **Conclusions:** This prospective study in patients with CS confirms that metyrapone effectively lowers UFC levels with a tolerability profile similar to the previously reported safety profile and improves QoL, at Week 12.

Neuroendocrinology and Pituitary
CLINICAL ADVANCES IN PITUITARY DISEASES

One-Year Outcomes of the Open-Label Extension of CHIASMA OPTIMAL, a Phase 3 Study of Oral Octreotide Capsules in Acromegaly