the diagnosis of adrenal adenoma in patients compared to the referent subjects from the same population **Methods:** Using a medical records linkage system, we identified adult patients living in the Olmsted County, MN diagnosed with an adrenal adenoma during 1995–2017. Patients with overt hormone excess were excluded. Every patient with adenoma was matched by sex and age to a referent subject from the same population. Subjects were followed until death or end of the study. Mental health related comorbidities and sleep disorders were assessed at baseline and during follow up. **Results:** Our cohort included 1004 patients with adrenal adenomas and 1004 referent subjects (58% women, median age of 63 years). Patients were more likely to smoke (70% vs 54%, p <0.001) and had a higher BMI (30 kg/m^2 vs 28 kg/m^2, p < 0.001). Within 5 years prior to the index date (diagnosis of adenoma), and after adjusting for BMI and smoking, patients demonstrated a higher prevalence of depression (Odds ratio, OR of 1.3 (CI95% 1.1–1.6), p=0.02), anxiety (OR of 1.4 (CI95% 1.1–1.8, p=0.003), substance abuse disorders (OR of 2.4 (CI 95% 1.7–3.4), p<0.001), but not insomnia (OR of 1.2 (CI95% 0.9–1.7) and sleep related breathing disorders (OR of 1.3 (CI 95% 0.9–1.7). During follow-up, starting 1 year after the diagnosis, patients demonstrated a higher risk of new onset depression (HR of 1.9, CI95%1.5–2.4), anxiety (HR of 1.5,CI95% 1.2–1.9), schizophrenia (HR of 1.7, CI95% 1.2–2.4), and substance abuse disorders (HR of 1.6, CI95% 1.2–2.0). Risk of sleep disorders 1 year after diagnosis was also high for insomnia (HR of 1.4, CI95% 1.1–1.9), sleep-related breathing disorders (HR of 1.8, CI95% 1.4–2.3), hypersomnias of central origin (HR of 2.0, CI95%1.04–3.96), parasomnias (HR of 2.4, CI95%1.2–4.7), and sleep-related movement disorders(HR of 1.9, CI95%1.3–2.6). **Conclusion:** Patients with adenomas are at increased risk for mental and sleep disorders, possibly explained by the underlying subtle cortisol secretion. Further prospective studies with an in-depth characterization of both hormonal secretion and mental/sleep disorders are needed. Reversibility or improvement of mental health and sleep disorders with adrenalectomy should be investigated.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Selective Serotonin Reuptake Inhibitors Increase Urinary Free Cortisol in Patients with Carney Complex and Primary Pigmented Nodular Adrenocortical Disease

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Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing syndrome predominantly associated with Carney Complex (CNC), a multiple endocrine neoplasia syndrome primarily caused by inactivating defects in *PRKAR1A*. PPNAD, which has neuroendocrine features, demonstrates cortisol production in response to serotonin as well as increased expression of tryptophan hydroxylase type 2, a serotonin synthesizing enzyme, and the serotonin (5-HT) receptors types 4, 6, and 7. This creates an autocrine/paracrine serotonergic regulatory loop that activates cortisol production. PPNAD can be diagnosed through a 6-day Liddle test (LT) showing a paradoxical increase of >50% from baseline in 24-h urinary free cortisol (UFC) on the 2nd day of high-dose dexamethasone administration (Day 6). Selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin and are widely used for the treatment of depression. We performed a retrospective cohort study of patients with CNC and PPNAD that underwent a LT to evaluate the effect of SSRIs on UFCs, with the hypothesis that SSRI use leads to an exaggerated increase in UFC through presumed activation of the described serotonergic regulatory loop. Of the 34 patients (4–65 y) with CNC and PPNAD that underwent a LT at our institution between 2004 and 2018, 4 took an SSRI during testing. No differences were observed between the SSRI (S) group and the non-SSRI (NS) group in baseline UFCs and the percent increase in UFC on D6. Specifically, the median (IQR) baseline UFC in the S group was 36 (13–252) mcg/24h (nl 4–56) vs 35 (13–98) mcg/24h in the NS group (*P*=0.95). The percent change in UFC was 208 (93–683)% in the S group and 185 (28–364)% in the NS group (*P*=0.89). However, there was a difference for overall UFC measurement (across days 1–6 of the LT) in the S group vs the NS group (P=0.03). Age <18 vs 18+ and sex did not have an effect on the outcomes (*P*=0.17 and *P*=0.74, respectively). Thus, we conclude that though the percent change in UFC during the LT was similar in both groups, there was a significant difference in overall UFC in the S group when compared to the NS group. These data support an effect of SSRIs and serotonin on UFC and consequently cortisol production in PPNAD. This interesting observation has to be confirmed in more patients with CNC and PPNAD to further elucidate the effects of SSRIs on cortisol production in patents with PPNAD-caused Cushing syndrome, as this may have significant diagnostic and therapeutic implications.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Significance of Discordant* Results: *between Confirmatory Tests in Diagnosis of Primary Aldosteronism

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Context: Current clinical guidelines recommend confirmation of positive result in at least one confirmatory test in the diagnosis of primary aldosteronism (PA). Clinical implication of multiple confirmatory tests has not been established, especially when patients show discordant results. **Objective:** The aim of the present study was to explore the role of two confirmatory tests in subtype diagnosis of PA.

Design: Retrospective cross-sectional study. **Setting:** The study was conducted at two referral centers. **Participants and Method:** We identified 360 hypertensive patients who underwent both captopril challenge test (CCT) and saline infusion test (SIT) and exhibited at least one positive result. Among them, we studied 193 patients with PA whose data were available for subtype diagnosis based on adrenal vein sampling (AVS). **Main Outcome Measure**: The prevalence of bilateral subtype on AVS according to the results of the confirmatory tests. **Results:** Of patients studied, 127 were positive for both CCT and SIT (double-positive), while 66 were positive for either CCT or SIT (single-positive) (n = 34 and n = 32, respectively). Altogether, 135 were diagnosed with bilateral subtype on AVS. The single-positive patients had milder clinical features of PA than the double-positive patients. The prevalence of bilateral subtype on AVS was significantly higher in the single-positive patients than in the double-positive patients. (63/66 [95.5%] vs. 72/127 [56.7%], P < 0.01). Several clinical parameters were different between CCT single-positive and SIT single-positive patients. **Conclusion:** Patients with discordant results between CCT and SIT have a high probability of bilateral subtype of PA on AVS.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Survival Benefit of Corticosteroid Replacement in Critically Ill Patients: One Treatment Effect or Two?

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Survival benefit of corticosteroid replacement in critically ill patients: one treatment effect or two?

Background: In the comparison of placebo versus corticosteroid replacement therapy (CRT) among ill patients, the treatment effect (difference in 28-day mortality rate between placebo and CRT) tends to vary according to mortality in the placebo group. In this context, we treat 28-day mortality in the placebo group as a surrogate for severity of illness [1]. **Hypothesis:** In the present era of physiologic CRT, critical illness related corticosteroid insufficiency (CIRCI) may be defined operationally by the difference in clinical outcomes, such as 28-day mortality, between placebo and CRT treatment groups. In this simulation analysis, we examined the hypothesis that treatment effects of CRT observed in various randomized, placebo-controlled clinical trials may be explained by heterogeneous population consisting of two strata, S1 and S2, having discrete conditional probabilities of mortality when treated with CRT vs. placebo. **Methods:** Using published Randomized Controlled Trial (RCT) data, the relationship between treatment effect and severity of illness was analyzed using a least squares solution weighted by sample sizes. A probability model included likelihoods for outcomes (28-day mortality with placebo vs. CRT) in two population strata: (i) a minority stratum (S1) having treatment effect > 0 and (ii) a majority stratum (S2) having a treatment effect ≤ 0. In a simple simulation scenario we varied the treatment effect in S1 as function of the placebo group mortality in S2 in order to fit the relationship obtained from published RCT data. The potential impact of sensitivity and specificity on diagnostic tests to identify S1 was also addressed. **Results:** A hyperbolic function (y = [Mx/(K+x)] - A) provided a good fit for published RCT trials of physiologic CRT (treatment effect [y] vs. placebo group mortality rate [x]). Pooling results for S1 and S2 having population frequencies of 0.2 and 0.8, respectively, approximated the observed hyperbolic function of treatment effects and severity of illness. A significant treatment effect was maintained when S1 was identified by diagnostic tests having 75% sensitivity-specificity. **Conclusions:** Population heterogeneity has not been excluded as an explanation for the relatively modest treatment effect of CRT in critically ill patients. Given the possibility of harm of CRT in the majority population (S2), our model further suggests that clinical or laboratory measures that would distinguish S1 and S2 with reasonable accuracy would significantly improve clinical outcomes and reduce numbers needed to treat. Our findings also support the more general hypothesis that the treatment effects of CRT vary according to severity of illness (1).

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Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

The Burden of Illness of Congenital Adrenal Hyperplasia (CAH) in Adults: Results: *of a Structured Literature Review*

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Objectives: Congenital adrenal hyperplasia (CAH) is a group of rare autosomal-recessive disorders that arise from genetic deficiencies in key enzymes involved in cortisol synthesis. The burden of CAH has never been comprehensively reviewed; this literature review was conducted to summarise the existing burden of illness evidence available for these patients. **Methods:** A structured, comprehensive literature review was conducted to identify articles describing the burden and treatment landscape of CAH. Literature databases (MEDLINE, Embase, the Cochrane Library and EconLit), websites and conference proceedings were searched. Searches were performed in 2016 and updated in June 2020; eligible articles presented evidence for patients with CAH or paediatric patients with adrenal insufficiency (AI), for ≥1 topic of interest (epidemiology; natural history; clinical characteristics; humanistic, caregiver and economic burden; treatment options; or clinical guidelines). The evidence presented here focusses on the humanistic and economic burden of CAH in adults. **Results:** A total of 3,711 citations were identified and 336 were included; 84 references reported humanistic or economic burden data relevant to adult patients with CAH. 51 publications were identified reporting patient symptoms,