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Background: A disruption in food motivation pathways has been described in females with anorexia nervosa (AN), a psychiatric disorder characterized by food restriction despite low weight. We have shown that in AN and healthy controls (HC), levels of oxytocin (OXT), a hormone involved in lactation, social behavior and weight regulation, decrease after a meal. In HC, we identified a relationship between postprandial change in OXT and subjective appetite, yet this association was absent in females with AN, suggesting a disconnect between OXT and appetite regulation in AN. Prior studies have shown that gray matter volume of the amygdala and hippocampus, areas rich in OXT receptors, correlate with OXT levels in HC. Furthermore, these regions play a central role in food reward and decreased volume has been reported in AN. We hypothesized that the relationship between postprandial change in OXT and amygdala and hippocampal gray matter volume would differ between AN and HC.
Methods: We performed a cross-sectional study of 51 females (23 restrictive AN; 28 HC). We drew blood for OXT levels fasting and 60 min after a standard meal and performed T1-weighted MRI scans of the brain in the fasted state. MRI data was quality controlled and processed with FreeSurfer. Average gray matter brain volumes were extracted from the bilateral amygdala and hippocampus for each subject. Linear regression models were used to determine differences between AN and HC of postprandial percent change in OXT on amygdala and hippocampus gray matter volume.
Results: Median [IQR] age was higher in females with AN (20.6 years [19.3, 21.5]) than HC (18.8 years [IQR 17.6, 20.3], p=0.02), and percentage of ideal body weight was lower in AN (75.5%) than HC (97.4%, p<0.01). Right hippocampus volume, adjusted for age and total intracranial volume, was significantly lower in AN (estimated difference -188 dm^3 [95%-CI -360, -17], p=0.04). Percent change in OXT was not different (p=0.5) but there was a trend for a positive interaction effect (p=0.08) for AN and percent change in OXT on right hippocampus volume. Posthoc exploratory analysis indicated a positive correlation in AN (R^2=0.41, p=0.02) and no correlation in HC (R^2=0.17,p=0.4) between percent change in OXT and right hippocampus volume. There was no significant between group difference in volume nor postprandial change in OXT for the bilateral amygdala or left hippocampus between groups.
Discussion: Our results indicate smaller right hippocampus volume and a trend towards a positive association with postprandial change in OXT in AN compared to HC. Future studies will be important to better define the relationships between OXT secretion and food motivation brain regions and the impact on eating behavior in AN.

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Resolution of Abnormal Gonadotropin Secretion After Surgical Cure in Men With ACTH-Dependent Cushing Syndrome

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Background: Hypothalamic-pituitary-gonadal (HPG) dysfunction is known to occur in male patients with Cushing Syndrome (CS) but the underlying mechanisms of HPG dysfunction remain unclear. We performed frequent blood sampling and GnRH stimulation tests to assess gonadotropin secretion in males before and after surgical cure of CS. **Methods:** We evaluated eight males age 32.5±12 years (mean ± SD) enrolled for surgical cure of ACTH-dependent CS at a tertiary care research center. Urinary free cortisol (UFC) was measured before and after surgery. Blood was sampled every 20 minutes for 24-hours with measurement of LH and FSH, before and 2 weeks to 160 weeks (median 80 weeks) after surgery. Patients received 100 μg of gonadotropin releasing hormone (GnRH) iv with measurement of LH and FSH at 0, 10 and 20 min before and 15, 30, 45, 60, 120 and 180 min after administration. Non-normative data was log-transformed before analysis using paired two-tail t-tests. A p-value of <0.05 was considered significant. Gonadotropin values are expressed in U/L as equivalents of the 2nd International Preparation of human menopausal gonadotropins with normal adult male ranges of 6-26 and 5-25 IU/L for LH and FSH, respectively. **Results:** Mean UFC was elevated ~ 6 times above the upper normal limit before surgery and returned to the reference range after surgery. 24-hour LH rose from 7.82 ± 1.48 preoperatively to 13.07 ± 2.96 IU/L (mean ± sem) after surgery (p=0.026) while mean FSH was unchanged (8.48 ± 1.51 vs 6.92 ± 1.29, p=0.37). LH pulse frequency, a marker of pulsatile GnRH secretion, recovered from a subnormal value of 6.88 ± 0.55 pulses/24 hr before to 12.13 ± 0.72 pulses/24 hr after surgery (p<0.0001) while LH pulse amplitude did not change (6.47 ± 1.21 vs 4.76 ± 0.88 IU/L, p=0.21). In response to GnRH there was a robust increase in LH that was not affected by curative surgery for CS (27.0 ± 7.2 vs 21.2 ± 7.6 IU/L; p=0.14) as was also the case for FSH (3.7 ± 1.2

vs 2.3 ± 0.5 IU/L; p=0.48), consistent with the absence of an effect of CS on gonadotroph responsiveness to LHRH. **Conclusion:** In men with Cushing Syndrome, hypogonadism is associated with inhibition of endogenous GnRH secretion but preservation of the pituitary response to GnRH. Hypothalamic suppression of the HPG axis is reversible after cure of CS.

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Testing of Adrenal Axis Function in Patients With Combined Pituitary Hormone Deficiency Caused by PROP1 Mutation

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Background: The mechanism of adrenal axis deterioration in PROP1 mutation remains uncertain and challenging. **Aim**: The aim of the project was to investigate the adrenal axis function in patients with combined pituitary function deficiency and PROP1 mutation. **Methods:** We performed the corticotrophin (CRH) stimulation test in 15 patients ((8W/7M) with confirmed CPHD due to the PROP1 mutation. 9/15 were familial cases from four families. Time of observation (ToO) was calculated since the first pituitary axis/ACTH insufficiency has occurred. The results were reported in the group with confirmed Adrenal Insufficiency (AI) and without AI defined as cortisol >18 ug/dl at any point during CRH test. ACTH is reported in pg/ml and cortisol in ug/dl, time of test is given in minutes (0‘, 15’,30’,45’,60’,120’). **Results:** The mean age of the group was 40,6 ± 12,1 years with mean 34,7 ± 10,3 years of CPHD observation (range 18 – 54 years). The In 5/15 the cortisol response met the criteria excluding AI. Among siblings there were patients both with/without AI. Both subgroups had similar ToO (without AI 35,6 ± 10,0 years vs 34,2 ± 10,3 years with AI). Mean time of AI duration was 15,0 ± 9,3 years. In the group of 5 patients without AI the mean morning cortisol was 12,48 ± 4,31 and ACTH was 31,26 ± 5,43. The mean maximal concentration of cortisol and ACTH were 24,94 ± 3,6 and 123,6 ± 39,9 respectively; Mean increase of cortisol was 12,46 ±4,04 and 92,34±34,48 for ACTH. In 10 patients with AI the mean morning cortisol was 3,33±1,39 and ACTH 22,71±6,75. The mean maximal concentration of cortisol and ACTH were 10,15±4,47 and 97,05 ± 59,15 respectively; Mean increase of cortisol was 6,83 ± 3,41 and 74,35 ± 53,72 for ACTH. For two patients high ACTH increase from 36,7 to 260 and from 28,65 to 112,0 was observed. Analysis of cortisol and ACTH response in both groups revealed that in group without AI the time of peak of ACTH was observed in 15’ (2/5) and 30’ (3/5) vs. in 15’(3/10), 30’(6/10) and 45’ in group with AI. The peak cortisol was observed in 30’, 45’ and 60’ (3/5) in group without AI vs 60’(6/10) or 120’ (4/10) in AI group. The mean maximal increase of ACTH was by 4,09±1,46 and 4,12±1,58 in AI group vs no AI group respectively. **Conclusions:** In patients with PROP1 mutation the adrenal axis can deteriorate long after other axis insufficiencies, however there are patients with no adrenal insufficiency even during lifelong observation. There is no specific order of deterioration even among affected siblings. In the vast majority of patients independently of cortisol increase there is ACTH response after CRH. Further studies on the pituitary function deterioration in patients with PROP1 mutation should be carried out to understand better the underlying mechanism and to set up the diagnostic timing and procedures.

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The Arginine Stimulation Test Allows Rapid Diagnosis of Central Diabetes Insipidus in Children

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Introduction: Water deprivation testing (H2O-dep) is usually required to distinguish between diabetes insipidus (DI) and primary polydipsia (PP) in children with polydipsia-polyuria syndrome (PP-S). The H2O-dep is challenging for children and their families. The prolonged fasting may provoke hypoglycemia and dehydration, particularly in younger children. Serum concentrations of copeptin (COP) (a surrogate marker of AVP, which is easier to measure by a robust assay), are known to increase in adults and children undergoing IV arginine (ARG) stimulation testing (ASTT).
Objective: To test the hypothesis that COP levels during ASTT would differentiate between DI and PP.
Methods: Serum COP responses to ARG were measured in 13 healthy short children being tested for GH deficiency (controls); and in 4 patients with PP-S. Arginine-HCl (500 mg/Kg) was infused IV from 0 to 30 min, with blood sampling at 0, 15, 30, 45, 60 min; seven of 13 controls also received clonidine PO (150 mcg/m2) at 0 min. COP was measured with a 2-site immunometric assay (BRAHMS Platform, Quest Diagnostics).
Results: A-Controls. As the COP values at each time point were similar in the ARG and ARG-Clonidine controls, the data from both groups were combined. COP peaked at 45-60 min post ARG in the 13 controls. COP (Mean+SD; pMol/l)) increased from 9.7+4.3, (range 3-17) to a peak of 12.4+5.0 (range 6-21) at 60 min; Δ% increase 47+50 % (range 0-133). The peak COP values on ASTT showed no correlation with subjects’ age or peak GH response.