Thyroid

HPT-AXIS AND THYROID HORMONE ACTION

Factors Associated with Reduced Thyroid Hormones in Cushing Syndrome Patients Before and After Surgical Cure

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SAT-449

Background: Hypercortisolemia adversely affects thyroid hormone secretion. We previously described the temporal pattern of thyroid function recovery in 23 patients (1). However, the factors leading to suppression and recovery of the hypothalamic-pituitary-thyroid (HPT) axis in Cushing's syndrome (CS) are not fully understood. We performed two separate studies to investigate these factors. Methods: In study 1, we examined patients (pts, n=62) with CS who underwent curative surgery and recorded their serum morning and evening cortisol, ACTH, tumor volume and duration of symptoms and 24-hour urine free cortisol (UFC) at baseline and the morning serum free T4, TSH and T3 at six-month intervals after cure. Data were log-transformed and Pearson correlations were performed. Linear mixed models were used to study factors that predict recovery of thyroid function. In study 2, we examined the diurnal variation of TSH by performing hourly TSH measurement between 3—7 PM and 12—4 AM on a cohort of pts (n=45) before surgery. *Wilcoxon Signed-Rank* method was used for comparisons of mean TSH across time and Pearson correlations were performed on log-transformed data. P values <.05 were considered significant. Results: Study 1: In this larger cohort, we confirmed previous findings of suppressed or low normal fT4 and TSH values with active hypercortisolism, with normalization after cure that reflected changes in the T3:TSH, fT4:TSH and T3:fT4 ratios. There were inverse linear correlations between log10 UFC, serum AM and PM cortisol; and log10 TT3, fT4 and TSH before surgery. Independent negative prognosticators of circulating fT4 recovery included UFC greater than 1000mcg/day (nl: 3.5—45mcg/day), duration of symptoms of less than one year, and ACTH levels greater than 60pg/mL(nl: 5—45pg/mL) Study 2: The nocturnal (12 - 4AM) TSH surge was reduced, so that the difference in day and night TSH values was not statistically significant; this contrasts with the 30—50% nocturnal TSH increase above daytime values seen in healthy subjects. There was an inverse relationship between UFC and nocturnal TSH, daytime TSH and TBG values, but there was no direct relationship between UFC and percent changes in nocturnal TSH values. Conclusions: Our findings suggest that a deficit in TSH stimulation of the thyroid gland may explain the reduction in T3 and T4 levels. There is a dose-response relationship between various measures of hypercortisolemia and both thyroid hormones and the pattern of TSH secretion. Finally, the severity of hypercortisolism correlates with a longer time to recovery of the HPT axis in pts with CS after curative surgery. 1. Shekhar S et al. HPG and HPT Axes in Cushing Syndrome. J Endocr Soc, 3 S1, April May 2019

Neuroendocrinology and Pituitary

NEUROENDOCRINE & PITUITARY PATHOLOGIES

Prevalence of Self-Reported Endocrine Comorbidities in Hypothalamic Hamartoma Patients: Data from the Hope for Hypothalamic Hamartoma Survey

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SUN-295

Background: Hypothalamic hamartoma (HH) are rare, congenital, benign mass lesions in the ventral hypothalamus that can be asymptomatic or associated with gelastic seizures and treatment-resistant epilepsy. Central precocious puberty (CPP) is the main endocrine comorbidity (30-80% of cases). Other endocrine comorbidities have also been described that tends to occur after surgery. However, previous studies reporting its prevalence have shown inconsistent results because of the rarity of the disease, variability of follow-up, and lack of long-term endocrinologic assessment. **Aims:** To evaluate the self-reported prevalence of demographics and endocrine comorbidities in a large cohort of HH patients. **Methods:** Hope for HH is a volunteer-based nonprofit organization founded by parents of children with HH. This international survey was initiated, translated into multiple languages and distributed by mail and electronically to families of children with HH in the Hope for HH database after concerns were raised that there have been multiple ongoing comorbidities (including endocrine) that continues to be under-recognized. **Results:** In total, 257 HH patients (132M/125F, mainly between ages 4-35 years and from the US, Russia, UK, Australia, Canada, Germany and Kazakhstan) participated in the survey. Some patients had a secondary diagnosis of Pallister-Hall (7.0%), Lennox-Gastaut (1.95%), Prader-Willi (0.8%) and West (0.8%) syndromes. The majority of patients (n=163, 63.4%) underwent surgery (MRI-guided stereotactic laser ablation [n=61, 37.4%], endoscopic resection [n=31, 19.0%], transcallosal resection [n=30, 18.4%], stereotactic radiofrequency ablation [n=27, 16.6%], orbitozygomatic resection [n=9, 5.5%]) or gamma knife radiosurgery (n=28, 17.2%). After surgery and/or radiation, ~50% of patients were seizure-free but reported unchanged, poor or very poor quality of life (QoL), with fatigue (56.4%), heat intolerance (46.3%) and adipsia (21.8%) being the more common symptoms. Reported endocrine comorbidities include CPP (42%), hypothalamic obesity (35.0%), abnormal body composition (31.5%), central hypothyroidism (19.8%), osteopenia/osteoporosis with low BMD (12.8%), diabetes insipidus (11.3%), GH deficiency (10.5%), central adrenal insufficiency (10.5%), central hypogonadism (5.1%), and delayed puberty (4.7%), and 26.5% of patients were not seeing an endocrinologist. **Conclusion:** In contrast to previous studies reporting low prevalence, mild and transient endocrine comorbidities in HH patients (2,3), this survey suggests a greater prevalence of other non-CPP endocrine comorbidities with a substantial number of patients reporting unchanged or impaired QoL. Thus, long-term endocrinologic follow-up with the involvement of a

multidiscliplinary team is essential to diagnose early and treat these comorbidities in these patients.

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH - FROM HORMONES TO GAMETES

A Novel Oral Testosterone Therapy (TLANDO) Safely Restores Testosterone to Eugonadal Levels with Fixed Dose Treatment

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SAT-052

Most testosterone (T) replacement therapy (TRT) products have relied on dose titration to achieve eugonadal levels. However, dose titration in clinical practice can be time-consuming, expensive, and subject to errors. TLANDO (LPCN 1021) is a novel oral testosterone undecanoate (TU) product absorbed via the intestinal lymphatic pathway. A previous clinical study (NCT02081300) suggested that titration with TLANDO has little to no impact to improve PK profiles. The objective of this study was to assess whether fixed dose of TLANDO can restore testosterone to eugonadal levels. A 24 day, open-label, single-arm, multicenter study with TLANDO in hypogonadal men (NCT03242590) was conducted. Subjects (N=95) received 225 mg testosterone undecanoate orally twice a day (i.e., 30 minutes after morning and evening meals) for 24 days. On Day 24, blood samples were collected over a 24 hour period. The primary endpoint was the percentage of TLANDO-treated subjects who achieved a 24-hour average serum T concentration within the eugonadal range of 300 to 1080 ng/dL after 24 days of treatment. Mean peak serum T concentration was calculated based on daily TLANDO administration at Day 24. Key safety endpoints included incidence of adverse events (AEs), physical examination results, clinical laboratory test results, and changes in HCT, lipids, and PSA. Treatment compliance was calculated as a percentage of the amount of study drug used divided by the amount of study drug expected to be used. 94 subjects completed the study with mean age of 56.0 years, mean BMI 32.8 kg/m^2, and baseline T level 202 ± 75 ng/dL. 80% of subjects achieved a 24-hour average serum T concentration within the normal range at Day 24. The lower and upper bounds of the 95% confidence interval was 72% and 88% respectively. Following daily administration of TLANDO at Day 24, the mean peak serum T concentration was 1178 ± 484 ng/dL. The incidence of treatment emergent adverse events (TEAEs) was 21%. The most frequently reported TEAEs were blood prolactin increase (6.3%), weight increase (2.1%), headache (2.1%), and musculoskeletal pain (2.1%). No deaths were reported during the study. Increase in hematocrit (0.9%) and PSA (0.2 μg/L) was observed. Decrease in lipids was observed (-6.9 mg/dL for HDL, -1.5 mg/dL for LDL, -8.9 mg/dL for triglycerides, and -10.6 mg/dL for total cholesterol). Overall mean treatment compliance was 99.7 ± 4.9%. In conclusion, a twice-daily, fixed-dose of TLANDO (450 mg TU total daily dose) successfully achieved target serum T level and achieved a safety profile consistent with that of other approved TRT products.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

Hypercalcemia Secondary to Calcitriol and PTHrP Cosecretion Only Responsive to Hydroxychloroquine

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SAT-346

Background: Hypercalcemia of malignancy mediated by concurrent elevations in both 1,25-dihydroxyvitamin D (calcitriol) and parathyroid hormone (PTH)-related protein (PTHrP) is a rare phenomenon previously only reported with solid tumors. The preferred treatment for calcitriol-mediated hypercalcemia is glucocorticoid therapy and second-line therapy is traditionally ketoconazole. Hydroxychloroquine has previously been reported as efficacious only in cases of calcitriol excess related to sarcoidosis.
Clinical case: A sixty-two year-old female with a history of diffuse large B cell lymphoma, complicated by disease progression despite multiple treatment regimens over the preceding five years, developed acute hypercalcemia to a corrected value of 14.7 mg/dL (8.9-10.3). Work-up revealed a suppressed PTH, PTHrP <2.0 pmol/L (0.0-3.4), and calcitriol elevation of 136.0 pg/mL (19.9-79.3). She was treated with zolendronate with rapid normalization of calcium levels. Upon recurrence of hypercalcemia six months later, repeat calcitriol was 176.0 pg/mL with a new PTHrP elevation of 7.0 pmol/L. Repeat dosing of zolendronate was less efficacious. She was prescribed prednisone 60 mg daily with subsequent addition of denosumab 120 mg weekly with continued hypercalcemia. Given rising levels of calcitriol and PTHrP (up to 285.6 pg/mL and 43.5 pmol/L, respectively) and potential drug interactions between ketoconazole and her chemotherapy, she was started on hydroxychloroquine 400 mg daily. Her calcium normalized and calcitriol dropped to 61.1 pg/mL despite imaging evidence of continued lymphoma progression. Three weeks later, she developed septic shock and was transitioned to hospice.
Conclusion: In reviewing the literature, this appears to be the first reported case of a hematologic malignancy with pathologic levels of both calcitriol and PTHrP. It is also the first reported efficacy of hydroxychloroquine in malignant hypercalcemia. Interestingly, PTHrP secretion occurred months after the initial development of hypercalcemia. Control of both calcitriol and calcium levels did not occur until initiation of hydroxychloroquine despite preceding use of high-dose glucocorticoids and anti-resorptive therapy. Our case suggests that hydroxychloroquine should be considered in cases of calcitriol-mediated hypercalcemia resistant to glucocorticoids, particularly as it has less drug