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Introduction: Evidence pertaining to new-onset endocrine dysfunction in patients with COVID-19 is currently limited and extrapolated from prior SARS epidemics. Further, identifying whether the quantum of this dysfunction is associated with the severity of disease in patients with COVID-19 is unknown. We aimed to to comprehensively explore the prevalence, nature and degree of endocrine dysfunction stratified based on disease severity at a dedicated COVID care centre.
Patients and Methods: Consecutive patients enrolled at PGIMER Chandigarh, were stratified on the basis of disease severity as: group I (moderate to severe disease including oxygen saturation <94% on room air or those with comorbidities) and group II (mild disease, with oxygen saturation >94% and without comorbidities). Hypothalamo-pituitary-adrenal, thyroid, gonadal axes and lactotroph function were evaluated. Inflammatory and cell-injury markers were also analysed.
Results: Patients in group I had higher prevalence of hypocortisolism (38.5 vs 6.8%, p=0.012), lower ACTH (16.3 vs 32.1pg/ml, p=0.234) and DHEAS (86.29 vs 117.8µg/dl, p= 0.086) as compared to group II. Low T3 syndrome was a universal finding, irrespective of disease severity. Sick euthyroid syndrome (apart from low T3 syndrome) (80.9 vs 73.1%, p= 0.046) and atypical thyroiditis (low T3, high T4, low or normal TSH) (14.3 vs 2.4%, p= 0.046) were more frequent in group I than group II. Male hypogonadism was also more prevalent in group I (75.6% vs 20.6%, p=0.006) than group II, with higher prevalence of both secondary (56.8 vs 15.3%, p=0.006) and primary (18.8 vs 5.3%, p=0.006) hypogonadism. Hyperprolactinemia was observed in 42.4% patients, without significant difference between both groups.
Conclusion: COVID-19 can involve multiple endocrine organs and axes, with a greater prevalence and degree of endocrine dysfunction in those with more severe disease. Involvement of multiple axes, particularly at hypothalamo-pituitary level suggests the possibility of hypophysitis as an underlying etiology. We also observed less characterised findings like atypical thyroiditis and normal DHEAS despite secondary hypocortisolism. Follow-up surveillance of these patients at periodic intervals and estimation of anti-pituitary antibodies could be considered to elucidate viral cytopathic effect or inflammation as the major underlying mechanism of endocrine dysfunction.

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Gonadotropin-Releasing Hormone Agonist Induced Pituitary Apoplexy

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Background: Gonadotropin-releasing hormone agonists (GnRHa), used in the treatment of prostate cancer (PC) and for reproductive purposes in women, have been implicated as the cause of pituitary apoplexy (PA), a potentially life-threatening condition. The pathophysiology of PA after GnRHa has not been completely elucidated. Proposed mechanisms include a stimulatory effect of GnRHa on pituitary adenoma cell metabolism, causing mismatched blood supply prompting hemorrhage or infarction. Prior documentation of PA associated with GnRHa has been scarce and limited to case reports.
Methods: This is a detailed clinical case series of GnRH-induced PA from a single institution, obtained by a Research Patient Data Repository query. Clinical characteristics of the patients including demographics, detailed history, time interval between GnRHa and PA, physical exam, biochemical data, pituitary imaging and pathology were reviewed.
Results: Seven cases were identified between 1990-2020; six men (aged 55 – 83 years) receiving treatment for PC and one woman (aged 22 years) receiving GnRHa for oocyte donation. All patients presented with headache; four within 48 hours of, one >1 month after, and one 5 months after, receiving GnRHa. One patient had insufficient data on time between GnRHa and PA. Most patients (86%) presented with nausea and vomiting. Other symptoms included ophthalmoplegia (43%), visual field defects (17%), and altered consciousness (29%). All patients had sellar masses and/or evidence of hemorrhage on MRI. Five patients underwent pituitary surgery while the others were managed medically. Of those who underwent surgical resection, 80% had positive histopathological staining for gonadotropins. Five patients with reliable hypothalamic-pituitary-adrenal (HPA) axis testing had impairment of this axis after PA; 40% recovered adrenal function. Central hypothyroidism occurred in 60% of whom 66% recovered. Hyponatremia occurred in 43%.
Conclusions: Patients with gonadotrope-secreting adenomas may develop PA in response to GnRHa, more frequently in elderly men who are receiving GnRHa treatment for PC. This may be due to older age and higher prevalence of GnRHa use in this group. However, as demonstrated here and in prior case reports, women are not exonerated from this complication. Headache and adrenal insufficiency are typically present. HPA axis recovers in a subset. While most patients present <48 hours after GnRHa treatment, delayed presentations may occur. Therefore, a history of prior GnRHa exposure should be ascertained in patients presenting with PA. While the incidence of PA after GnRHa is low, this case series and prior case reports suggest that this serious potential complication should be recognized prior to treatment, especially in patients with known pituitary macroadenomas.

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Growth Hormone Releasing Hormone Reduces Plasma Markers of Immune Activation and Hepatic Immune Pathways in Nonalcoholic Fatty Liver Disease

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Introduction: The GH/IGF-1 axis affects multiple metabolic pathways, and animal models demonstrate that it also modulates immune function. Little is known, however, regarding effects of augmenting GH secretion on immune function in humans. This study used proteomics and gene set enrichment analysis to assess effects of a GH releasing hormone (GHRH) analog, tesamorelin, on circulating immune markers and immune-related gene pathways in the liver in people with HIV (PWH) and NAFLD. We hypothesized that tesamorelin would decrease circulating markers of immune activation in conjunction with previously reported reductions in visceral fat and hepatic triglyceride. **Methods:** 92 biomarkers associated with immune function (Olink Immuno-Oncology panel) were measured in plasma samples from 61 PWH with NAFLD who participated in a double-blind, randomized, 12-month trial of tesamorelin versus identical placebo. Proteins differentially altered by tesamorelin at a false discovery rate < 0.1 were considered significantly changed. Gene set enrichment analysis targeted to immune pathways was subsequently performed on liver tissue from serial biopsies. **Results:** Compared to placebo, tesamorelin decreased circulating concentrations of 13 proteins, including four chemokines (C-C Motif Chemokine Ligands 3 [CCL3, effect size -0.38 Log_2 fold change], 4 [CCL4, -0.36 Log_2 fold change], and 13 [CCL13 or MCP4, -0.42 Log_2 fold change] and interleukin-8 [-0.50 Log_2 fold change]), two cytokines (interleukin-10 [-0.32 Log_2 fold change] and cytokine stimulating factor 1 [-0.22 Log_2 fold change]), and four T-cell associated molecules (CD8A [-0.37 Log_2 fold change], Cytotoxic And Regulatory T Cell Molecule [CRTAM, -0.47 Log_2 fold change], granzyme A [-0.53 Log_2 fold change], and adhesion G protein-coupled receptor G1 [ADGRG1, -0.54 Log_2 fold change]), as well as arginase-1 [-0.95 Log_2 fold change], galectin-9 [-0.26 Log_2 fold change], and hepatocyte growth factor [-0.30 Log_2 fold change]. No proteins in the panel were significantly increased by tesamorelin. Network analysis indicated close interaction among the gene pathways responsible for the reduced proteins, with imputational analyses suggesting down regulation of a closely related cluster of immune pathways. Targeted transcriptomics using tissue from liver biopsy confirmed an end-organ signal of down-regulated immune pathways, including pathways involved in antigen presentation, complement activation, toll like receptor and inflammatory signaling, and T-cell activation. **Conclusions:** Long-term treatment with tesamorelin decreased circulating markers of T-cell and monocyte/macrophage activity, with corresponding downregulation of immune pathways in the liver. These findings suggest that augmenting pulsatile GH may ameliorate immune activation in a population with metabolic dysregulation and systemic inflammation.

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Long-Term Corticotroph Function Following Cure of Cushing's Syndrome

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Introduction: Hyper- and hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis in Cushing's syndrome (CS) and Addison's disease (AD) is associated with disturbances of classical feedback mechanisms. Time to recovery of adrenal function after CS remission depends on the etiology of CS and is longest after adrenal CS. To date there are no data on the recovery of corticotroph function following CS remission, and the synacthen test is recommended for testing adrenal function in patients with hypopituitarism. **Aim** Here we aim to test corticotroph function after long-term cure of Cushing's syndrome following bilateral adrenalectomy (BADx), compared to patients with primary glucocorticoid deficiency due the presence of 21-hydroxylase antibodies or adrenoleucodystrophy, a pathophysiological model of glucocorticoid and mineralocorticoid deficiency. **Methods:** We retrospectively evaluated data from patients with CS and AD attending our endocrine department between 2000 and 2020, using the following inclusion criteria: BADx performed for pituitary/ectopic/adrenal or occult CS or primary adrenal insufficiency confirmed either by the presence of 21-hydroxylase antibodies or genetically in adrenoleucodystrophy. **Results:** Full data were available for 93 patients: 43 patients with BADx due to CS (18 patients with pituitary CS, 14 patients with adrenal CS and 11 patients with ectopic/occult CS, F:M 29:14, mean age at BADx 45.4 years age range 13-74 years) and 50 patients with AD (47 cases with positive 21-hydroxylase antibodies, 3 cases with adrenoleucodystrophy, F:M ratio 27:23, mean age at diagnosis 35 years, age range 6-57 years). The observation period was 537.5 patient-years after BADx (mean 12.5 years, range 1-38 years) and 647 patient-years following AD diagnosis (mean 14.2 years, range 1-46 years). At the last visit, there were no differences between the hormone substitution regimes between the groups. ACTH concentrations during the whole observation period and also at the last visit were lowest in patients with adrenal CS (56.5 pg/ml) when compared to patients with AD (487 pg/ml, $p<0.001$), or with patients with pituitary CS (377.5 pg/mL, $p=0.011$). ACTH values in patients with AD in long-term follow-up were significantly higher when compared to all patients with CS (141 pg/mL, $p<0.001$). **Conclusion:**