

of prednisolone (or equivalent doses) daily for longer than 4 weeks) admitted to hospital very unwell with confirmed or suspected COVID recommendations is to start on Hydrocortisone 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h per intravenous or IM bolus injection). **Method:** Retrospect data collection on Patients admitted in May 2020 to Bedford Hospital with suspected or confirmed COVID 19 disease with adrenal insufficiency or on long term steroid use. Those patients should be started on Hydrocortisone 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h per intravenous or IM bolus injection).

Results: In May 2020, 295 patients admitted under the medical team in Bedford Hospital with confirmed or suspected COVID-19. Only 12 patients met the inclusion criteria, one patient with a diagnosis of Addison disease and the remaining 11 patients on long term steroids. None of these patients were managed as per updated guidelines. 6 patients had less than the adequate dose, they were started on prednisolone 30-40mg. 4 patients dose of oral steroids was only doubled, 1 patient received the same dose of oral steroid and the only confirmed Addison had higher dose of hydrocortisone. Moreover, In June 2020, The RECOVERY Outcome trial results showed that Dexamethasone 6mg for 10 days reduces the death by one third in hospitalised patient with severe respiratory complications of COVID-19. Dexamethasone 6mg is 12 times the physiological required steroid dose, this is equivalent to 240mg hydrocortisone, which is adequate for steroid replacement in patients with adrenal insufficiency or suppression.

Conclusion: In view of these results and the outcome of the RECOVERY Trial, Local trust guidelines updated, indicated that any patient with Adrenal insufficiency or suppression including those on long term steroids very unwell admitted to the hospital should receive Dexamethasone if requiring oxygen or Hydrocortisone if not requiring oxygen. Recommendation of changes included teaching sessions delivered to doctors, posters on updated guidelines distributed in major areas in hospital and trust guidelines updated on the intranet.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Changes in Adrenal and Gonadal Androgens After 14-Day Treatment With CRF1 Receptor Antagonist, Crinicerfont (NBI-74788), in Men With Classic 21-Hydroxylase Deficiency

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Background: Congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency (21OHD) causes cortisol insufficiency and androgen excess. A phase 2 trial of crinicerfont, a CRF1 receptor antagonist, in 18 adults with 21OHD showed prominent decreases in ACTH, 17-hydroxyprogesterone, and androstenedione (A4), and in women, testosterone (T), after 14 days of treatment. In men with 21OHD, T derives from both adrenals and testes; in poor disease control, A4/T ratio is elevated due to disproportionately increased adrenal A4 production and decreased testicular T production. We sought to determine the impact of crinicerfont on both adrenal and gonadal androgen production in men with 21OHD in this phase 2 trial.

Methods: A4 and T data were analyzed for 7 men who completed 1 or more of 4 oral dosing regimens: Cohort 1, 50 mg QHS, n=4; Cohort 2, 100 mg QHS, n=2; Cohort 3, 100 mg QPM, n=5; and Cohort 4, 100 mg BID, n=3 (14 total treatment periods). Mean 0600-1000 4-hour morning window (M4hMW) and mean 24-hour (M24h) A4, T, and A4/T ratios were analyzed from serial serum samples at baseline and on day 15.

Results: Dose-dependent reductions in M4hMW A4 were observed [median (range)] in men, consistent with previously presented data in all subjects: Cohort 1: -21% (-84 to -12%); Cohort 2: -37% (-51% to -23%); Cohort 3: -43% (-85% to +140%); Cohort 4: -62% (-90% to -33%).

In contrast, M4hMW T showed inconsistent changes [median (range)]: Cohort 1: +18% (-40% to +82%); Cohort 2: -4% (-4.3% to -3.8%); Cohort 3: +9% (-11 to +24%); Cohort 4: +9% (-3% to +27%).

Thus, M4hMW A4/T ratios decreased with dose. Values at baseline, on day 15, and percent changes [median (range)] were, respectively: Cohort 1: 0.9 (0.3–2.6), 0.6 (0.1–2.1), -26% (-91% to +23%); Cohort 2: 5.0 (4.8–5.2), 3.3 (2.5–4.2), -35% (-49% to -20%); Cohort 3: 0.6 (0.1–6.9), 0.3 (0.1–2.7), -54% (-85% to +178%); Cohort 4: 3.9 (0.6–5.9), 0.4 (0.3–2.1), -65% (-92% to -31%).

M24h A4/T ratios similarly declined in all cohorts. Values at baseline, on day 15, and percent changes [median (range)] were, respectively: Cohort 1: 1.0 (0.3–2.3), 0.4 (0.1–1.9), -33% (-92% to +2%); Cohort 2: 4.3 (3.8–4.9), 2.7 (2.4–3.0), -36% (-51% to -22%); Cohort 3: 0.5 (0.1–4.7), 0.4 (0.1–2.4), -59% (-78% to +310%); Cohort 4: 3.2 (0.4–4.1), 0.4 (0.3–1.7), -58% (-89% to -31%).

Conclusions: Following crinicerfont therapy, A4 and A4/T decreased in a dose-dependent manner in men with 21OHD. In contrast to reductions in T observed in women with 21OHD, T did not change consistently and rose in some men. Preserved T values despite marked A4 reductions suggests testicular T production increased during crinicerfont therapy, perhaps due to release of gonadotropin suppression from adrenal-derived androgens. Long term studies are needed to determine if crinicerfont treatment improves additional measures of testicular function in men with 21OHD. **Reference:** RJ Auchus, et al. *J Endocr Soc* 2020;4(Suppl 1):OR25-03.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Changes in Clinical Presentation and Perioperative Management of Pheochromocytomas and

Paragangliomas: A Four-Decade Experience in a Academic Center

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Objective: Latin American reports on pheochromocytomas and paragangliomas (PPGL) are scarce. Recent studies have shown changes in both clinical presentation and management of these patients. We aimed to assess the main characteristics of PPGL patients in a single academic center over the last four decades. **Experimental design:** Cohort study. **Patients and methods:** Demographic, clinical, biochemical, genetic and perioperative data from 105 PPGL patients were retrospectively and prospectively collected over the 1980–2019 period. Patients were categorized into four groups (14 patients in the 1st, 25 patients in the 2nd, 27 patients in the 3th and 39 patients in the 4th decade) according to the date of diagnosis. **Results:** The mean age at diagnosis was 46±19 years, and the tumor size was 5.3±2.2 cm, female gender was 63%, bilateral tumor of 15%, paragangliomas 9% and metastatic disease in 15%. The aforementioned parameters remained stable across the four decades. During the study period we observed significant increases in doxazosin dosing (2.7±2.6 mg vs. 8.0±4.5 p<0.003) and laparoscopic procedures (28% vs. 84% p<0.001) along with a decrease in the length of hospital stay (10.0±8.9 vs. 3.8±1.7 days p=0.007). Among the 24 genetic tests performed, we identified 59% germline mutations. The most frequent mutations were RET (18%) and SDHX (18%), followed by VHL (14%), MAX (5%) and NF1 (4%). Notably, in the last decade we observed a dramatic increase in the proportion of incidental PPGL diagnosis (0% vs. 53% p<0.001) and genetic testing analyses (0 vs. 19 p<0.001). When comparing incidental diagnosis (n=25) versus clinically suspicious cases (n=50), incidentalomas had fewer adrenergic symptoms (38 vs. 62%; p<0.001), and lower rates of hypertension (64 vs. 80%; p=0.01), hypertension crises (28 vs. 44%; p=0.02), functionality (79 vs. 100%; p=0.01) and total catecholamines and/or metanephrine levels (8.4 vs. 12.5 fold above the upper normal limit; p=0.04). **Conclusions:** The implementation of a multidisciplinary program increased diagnosis and genetic testing and also optimized anesthesia and surgical procedure, translating into a notorious improvement in perioperative outcomes. In addition, we observed a change in the clinical presentation of PPGL in recent decades with a marked increase in incidental cases, which highlights the importance of early diagnosis and treatment.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Clinical and Pathological Features of Metastatic Adrenocortical Carcinoma

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Introduction: Adrenocortical carcinoma (AAC) is a rare and aggressive disease, associated with a poor prognosis. Surgery with complete resection (R0) remains the only curative treatment. However, even after complete resection, most patients present with distant metastatic disease. The aim of this study is to determine clinical and pathological features of metastatic disease in AAC. **Materials and methods:** Retrospective cohort study in 34 patients with AAC followed in our centre since 1991 until 2019. Selected patients with metastatic disease (n=21) and without metastatic disease (n=13). Descriptive and comparative data analyses. Statistics: SPSS@v.23, with the variables: age, sex, clinical signs and symptoms, hormonal activity, imaging and pathological characteristics, surgical procedure, postoperative adjuvant treatments and overall survival. **Results:** 27 (79%) female and 7 (21%) male patients were included in our study, with a median age of 50 ± 13 years at the time of diagnosis. 21 patients (61,2%) presented with metastatic disease (38% of which at the time of diagnosis) representing the metastatic disease group. 13 (38,8%) patients had no metastases until the collected data (group without metastatic disease). In the comparative analyses between the two groups, patients with metastatic disease had significantly more laparotomy procedures (71,2% n=15 vs 15,4% n=2; p<0,05), bigger tumours (≥ 12cm) (52,4% n=11 vs 23% n=3; p<0,05) and higher Ki67 (34,18% vs 1%, p<0,05). Postoperatively, the metastatic group had higher LDH (LDH at 6 months) (582 ± 502 vs 181 ± 47; p<0,05) and lower overall survival (months) (22,9 ± 4,69 vs 237,16 ± 44,42; p<0,05). Patients with metastatic disease had more constitutional symptoms (weight loss and asthenia) (33,3% n = 7 vs 15,4% n = 2; p = 0.092) and incomplete surgical resections (R1/R2) (42,8% n = 9 vs 15,4% n = 2; p=0.18), however, without statistical significance. There were no differences regarding: age, sex, hormonal activity, imaging characteristics and post-surgical medical treatment. **Conclusion:** In this study, the adrenocortical carcinoma metastasis rate was 61,2% with an overall survival of 23 months in the metastatic group. Laparotomy surgeries, tumour size ≥12cm and higher KI67 are features significantly associated with metastatic disease in adrenocortical carcinoma. Constitutional symptoms and incomplete surgical resections are more common in metastatic patients, however without statistical significance, in this cohort.

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