Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Posterior Hypothalamic Involvement on Pre-Operative Magnetic Resonance Imaging as a Predictor for Hypothalamic Obesity in Craniopharyngiomas

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MON-LB45

Craniopharyngioma (CP) is a rare embryonic tumor of the sellar and parasellar region with benign histology (World Health Organization grade I) thought to arise from embryonic remnants of Rathke's pouch. Despite its high survival rates, this tumor can lead to severe morbidity secondary to destruction of adjacent structures. Hypothalamus (HT) is a brain region that has a central role in regulating body weight through a complex mechanism involving central and peripheral signaling pathways. Destruction of its distinctive nuclei induces hyperphagia, hyperinsulinemia and weight gain. Seventy-five patients with CP who underwent first surgical resection in a single center by the same neurosurgeon between February 2005 and March 2019 were screened; those who have had prior radiation, were aged below 18 years, or did not have follow up body mass index (BMI) after surgery were excluded. Ultimately, this study included 45 patients with a mean age 50.5 years, 73.3% women. Pre and post-operative MRI were independently reviewed by three neuroradiologists to determine involvement of the hypothalamic regions: anterior, anterior and posterior, or no hypothalamic involvement. Body mass index were recorded pre operatively and subsequently after TSS up to 24 months post operation. Association between hypothalamic region involvement and BMI as well as endocrine function were examined. Posterior hypothalamic involvement seen in pre operative MRI (N=28) was significantly associated with higher BMI at 3-6 month, 7-12 month, and 13-24 month follow up ($p < 0.05$) in comparison to involvement of anterior hypothalamic alone or no hypothalamic involvement. Similarly, posterior hypothalamic involvement in the pre and post-operative MRI was significantly associated with development of diabetes insipidus (DI) ($p < 0.05$) compared to anterior or no hypothalamic involvement. There was no association between pre-operative BMI and hypothalamic involvement. Although the weight gain was accelerated after surgery, there was no association between post operative MRI and ensuing BMI, suggesting that the damage of the hypothalamic nuclei was done by the CP rather than surgical procedure. Conclusion: Assessment of hypothalamic involvement by anterior and posterior regions on pre operative MRI can be helpful in predicting development of obesity in patients with CP.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS III

A Case of Synchronous Non-Functioning Paraganglioma of the Urinary Bladder and Prostate Cancer

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SAT-LB306

• Introduction

The bladder is an uncommon site for a paraganglioma, with only <1% of all paragangliomas occurring in the bladder. Management of non-functioning bladder paraganglioma is uncharted due to its rarity, and there is even less data for cases with synchronous malignancy. We found two case reports of synchronous paraganglioma and prostate cancer, only one in the bladder. Here we report a second case and discuss management.

• Clinical Case

A 72-year-old man with high risk prostate cancer, Grade group 5 on biopsy, was found to have a 1.2 x 1.6 cm bladder wall mass on staging CT scan. The transmural mass was only partially resectable via transurethral approach. Pathology unexpectedly revealed paraganglioma, confirmed by immunohistochemical stains for Synaptophysin, Chromogranin, and CD56.

The patient had longstanding hypertension controlled on losartan and denied any symptoms of catecholamine excess. He had no family history of paraganglioma, pheochromocytoma, or related neoplastic syndrome. Plasma free metanephrine and normetanephrine levels were 57pg/mL (normal 57pg/mL) and 157pg/mL (normal 148pg/mL), respectively. Urinary studies were not performed due to stage 4 chronic kidney disease.

Staging CT scan and bone scan did not show any other lesions. Even in cases of known distant metastases of paraganglioma, surgical resection of all tissue is recommended if possible. Thus, he underwent radical prostatectomy, bilateral pelvic lymphadenectomy and partial cystectomy. Prostate cancer was downgraded to Grade group 2, pT3aN0Mo and complete excision of the paraganglioma was confirmed.

Evaluating for metastases and follow up are challenging in all paraganglioma cases, but especially non-functioning paragangliomas. Bladder paragangliomas carry a 10-15% risk of malignancy, but no separate data is reported for non-functioning ones. Histology scoring systems that are somewhat predictive in pheochromocytoma are less helpful in paragangliomas. Imaging is also challenging. CT, MRI, and a variety of functional imaging modalities have sensitivities for paraganglioma metastases in the range of 50 – 94% depending on location, functionality, and presence of germline mutation. For now, we recommend non-contrast CT with ^{18}F-fluoro-2-deoxy-2-D-gluocse (FDG) PET. Though guidelines recommend annual biochemical surveillance, the usefulness in non-functioning paraganglioma is questionable.

Genetic testing is recommended for all patients with paraganglioma. Succinate dehydrogenase B (SDHB) is

most important given the propensity for metastases. Thus, we recommended the SDHx germline mutation package.

• Clinical Lesson

This case is the second reported synchronous bladder paraganglioma and prostate cancer. It highlights the challenge, lack of data, and need for advancement in our knowledge for the best management of incidental, non-functioning, extra-adrenal paragangliomas.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Nutritionally-Induced Alteration in KNDy Neuronal Expression in the Arcuate Nucleus of Ewes

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SUN-LB54

Kisspeptin, neurokinin B, and dynorphin are imperative for GnRH/LH pulsatility and reproductive cyclicity. Neurons co-expressing these neuropeptides, KNDy neurons, within the arcuate nucleus of the hypothalamus (ARC) are positioned to integrate energy balance signals from neuronal and glial cells. Energy balance mediates neurokinin B expression in the ARC and LH pulse amplitude. Dynorphin mediates progesterone negative feedback on GnRH neurons. The hypothesis that the number of KNDy-expressing neurons in the ARC of ewes during the luteal phase of the estrous cycle is influenced by energy balance was tested using ovary-intact, mature ewes fed to lose, maintain, or gain body weight. Fluorescent multiplex immunohistochemistry was employed to identify and quantify neurons expressing a single neuropeptide and co-expressing kisspeptin, neurokinin B, and dynorphin in the ARC. Kaminski et al. (1) reported previously that concentrations of insulin and leptin differed between ewes fed to achieve different body weights and that ewes fed to gain body weight had increased concentrations of progesterone in the luteal phase of the estrous cycle. Moreover, tanycyte density and cellular penetration into the ARC are increased in ewes fed to gain body weight (2). Number of neurons in the ARC expressing kisspeptin (14.9 ± 2.7 neurons, 20.9 ± 3.6 neurons, and 51.5 ± 3.3 neurons in ewes fed to lose, maintain, and gain body weight, respectively), neurokinin B (21.5 ± 3.2 neurons, 31.3 ± 4.3 neurons, and 56.0 ± 3.9 neurons in ewes fed to lose, maintain, and gain body weight, respectively), and dynorphin (10.1 ± 2.4 neurons, 14.9 ± 3.2 neurons, and 33.1 ± 2.9 neurons in ewes fed to lose, maintain, and gain body weight, respectively) protein was increased ($P < 0.0001$) in ewes fed to gain body weight. Number of KNDy neurons in the ARC expressing kisspeptin, neurokinin B, and dynorphin protein was decreased in ewes fed to lose body weight (1.0 ± 0.5 neurons; $P = 0.01$) and increased in ewes fed to gain body weight (6.7 ± 0.6 neurons; $P = 0.0005$) when compared to ewes fed to maintain body weight (3.3 ± 0.7 neurons). These findings suggest that expression of kisspeptin, neurokinin B, and dynorphin protein in the ARC during the luteal phase of the estrous cycle may be influenced by nutritionally-induced alterations in circulating concentrations of progesterone that drive changes in morphology and density of tanycytes. Moreover, these results demonstrate that changes in KNDy neurons within the ARC occur as an adaptation to energy balance, potentially regulated divergently by metabolic milieu.

References: (1) Kaminski et al., Theriogenology. 2015 83:808-16. (2) Prezotto et al., Domestic Animal Endocrinology. 2020 Accepted.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Lithium: The Culprit of Multiple Endocrinopathies

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MON-LB65

Background: Lithium, commonly used to treat various psychiatric disorders such as bipolar disorder, can cause acute toxicity that presents with nausea, vomiting and diarrhea. Lithium can also cause life-threatening endocrine abnormalities, including hypercalcemia, hypernatremia, and both hypo- and hyperthyroidism.

Clinical Case: A 61-year old female with hypothyroidism, bipolar disorder, hyperparathyroidism with two-gland parathyroidectomy on lithium for over 30 years presented with altered mental status.

Initial labs revealed elevated creatinine 1.92 mg/dL (0.8-2.00mg/dL) compared to baseline 0.82 mg/dL, sodium 154 mg/dL (135-147 mg/dL), Corrected calcium 11.7 mg/dL (8.5-10.5 mg/dL), PTH 96 pg/mL (15-65 pg/mL), and high lithium levels 1.45 mmol/L (0.60-1.20 mmol/L). Further studies showed hypotonic polyuria with no increase in urine osmolality after desmopressin, consistent with nephrogenic diabetes insipidus. Lithium was held and she was treated with aggressive intravenous hydration with dextrose 5% water.

Hypercalcemia is thought to result from increased secretion of PTH due to an increased set point at which calcium suppresses PTH release; this often resolves once lithium is stopped. Lithium can also unmask previously unrecognized mild hyperparathyroidism, and/or raise serum PTH concentrations independent of calcium levels.[1] The drug interferes with the kidneys' ability to concentrate urine in the collecting tubules by desensitizing response to antidiuretic hormone, causing diabetes insipidus. The resulting volume depletion from excessive urinary water loss in turn lead to acute kidney injury and hypernatremia.[2] Hypothyroidism results from lithium-inhibited synthesis and release of thyroid hormones and decreases iodine trapping.

Conclusion: Although these are infrequent complications of lithium use, they remain pertinent clinical findings to consider due to their morbidity. In this case, our patient may have avoided multiple chronic electrolyte abnormalities leading to altered mental status if lithium toxicity had been recognized earlier.