Neuroendocrinology and Pituitary

CASE REPORTS IN UNUSUAL PATHOLOGIES IN THE PITUITARY

Atypical Teratoid Rhabdoid Tumor of the Sellar Region: An Unusual Cause of Hypopituitarism

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Background: Atypical teratoid/rhabdoid (AT/RT) tumor of the sellar region is an extremely rare malignant tumor in adults. To date, there are no definitive guidelines for optimal treatment and the prognosis of this tumor is poor. The pituitary insufficiency was rarely mentioned in previous literature and might be overlooked.

Clinical case: A 43 years old female presented to our clinic with severe periorbital pain. The magnetic resonance imaging of the brain revealed a 1.5x1.5x 3 cm sellar mass which showed inhomogeneous enhancement after gadolinium administration. Hormonal work up showed 8AM cortisol of 1.86 mcg/dL, free T4 1.0 (0.8–1.8 ng/dL), TSH 0.05 (0.3 - 4.1 uIU/ml), FSH 6.0 (1.6–9.3 IU/L), LH 1.8 (2.4–9.3 IU/L), estradiol <18.35 (80–790 pmole/L), IGF-1 96.6 (50.6–263.7 ng/ml), prolactin 56.6 ng/ml.

She underwent transsphenoidal surgery with tumor removal. The pathological result showed a mixture of pleomorphic spindle cell, oval shape tumor and poorly differentiated cell. The tumor was negative for INI1 (SMARCB1) compatible with AT/RT WHO grade IV. She developed pan hypopituitarism after surgery. She received 6 courses of 5950 cGy/25 fractions cranial irradiation and 6 courses of ifosfamide, cisplatin and etoposide. She completed the treatment regimen without significant toxicity. She continued hormonal replacement for panhypopituitarism and is still being followed at our clinic for 4 years without tumor progression or other complications.

In previously reported cases, all of the sellar AT/RT were female with a median age of 45 years old (range 20–61). The clinical presentations are rapidly enlarged sellar mass with compressive symptoms to the adjacent structures. The radiological findings of sellar AT/RT are non-specific. The diagnosis is based on histopathological findings. Presence of rhabdoid cells on histopathology and polyphenotypic immunopositivity for epithelial, mesenchymal, and neuroectodermal markers along with loss of expression of *SMARCB1/INI1* help in establishing a diagnosis of AT/RT. Currently, there are no definitive guidelines for optimal treatment. Multimodality treatment consisted of surgery, radiation and chemotherapy are the mainstays of treatment of the AT/RT. Of the 16 adults reported in the literature, 9 patients survived more than 12 months resulted in 47% of one-year survival rate. To our knowledge, this case is the sellar AT/RT with the longest survival to date.

Conclusion: AT/RT is one of the most aggressive tumors in the sellar area. Due to its aggressiveness, hypopituitarism is anticipated. Our patient had postoperative secondary adrenal insufficiency, secondary hypothyroid and hypogonadotropic hypogonadism. Apart from multimodality treatment required for tumor control, pituitary hormones should be evaluated preoperatively to prevent perioperative mortality and long-term improvement in the quality of life.

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL GLUCOSE METABOLISM AND DIABETES

A Framework for Understanding and Managing 'The Diabetes Syndrome': A Unified Pathophysiologic Approaching the Context of the Beta-Cell Classification of Diabetes

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We have previously presented a proposal for a new, beta-cell centric classification of diabetes based on a consilience of genetic, metabolic, and clinical research that have accrued since the current classification was instituted. It recognizes that the beta-cell is THE core defect in all patients with diabetes. Differences in the genetics (and epigenetics), insulin resistance, environment and inflammation/immune characteristics resulting in the damage to the beta-cell in each individual will determine the phenotypic presentation of hyperglycemia and allow for a patient-centric, precision-medicine therapeutic approach, part of which we labeled 'the Egregious Eleven'.

We now recognize the same pathophysiologic mechanisms that account for damage to the beta-cells govern the susceptibility of the cells involved in the complications and other conditions 'tied to' diabetes to damage by the abnormal metabolic environment that typifies beta-cell dysfunction and 'fuel excess'. This abnormal metabolic environment is typified by oxidative stress which alters metabolic pathways (a la Brownlee's Hypothesis model), alterations in gene expression, epigenetics, and inflammation. This allows us to understand the varied risk of developing complications of diabetes, including malignancies, dementia, NASH, psoriasis with similar levels of glycemic control; how non-glycemic effects of some medications for diabetes result in marked complication risk modification; and the value treating co-morbidities of diabetes in modifying complication risk.

Principles we outlined in using 'the Egregious Eleven' model- use agents that preserve beta-cell function, treat with least number of agents that treat most number of mechanisms of hyperglycemia- can be extended to use those agents, in combination, that also engender weight loss, decrease CV outcomes and have real or potential benefits in cancers related to diabetes, dementia risk, NASH, psoriasis. This approach allows for a more accurate assessment of each patient's disease and effecting true precision medicine

Schwartz, S, et al, Diabetes Care 2016, 39:179–186.
Schwartz SS, et al Trends Endocrinol Metab. 2017;28(9):645–655.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Estradiol Changes Angiotensin II-Induced ERK1/2 Phosphorylation by Different Pathways in the Hypothalamus and Lamina Terminalis

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Female gonadal hormones, especially 17β-estradiol (E2), are known to mediate hydromineral homeostasis and blood pressure mainly by attenuating renin-angiotensin system (RAS) actions. The RAS plays an essential role in the maintenance of hydromineral and cardiovascular homeostasis via angiotensin II (ANGII), a key component of the RAS. However, the cellular mechanisms of the interaction between E2 and ANGII and its physiological role are not fully elucidated. Recently, our group showed that ERK1/2 is involved in sodium intake and vasopressin release induced by ANGII in female rats. In addition, E2 decreases ERK1/2 phosphorylation induced by ANGII in the hypothalamus and in structures of the lamina terminalis (LT). Thus, the goal of the present study was evaluated some mechanisms that could be involved in ERK1/2 dephosphorylation induced by E2 in response to ANGII, such as MAPK phosphatase 1 (MKP-1) and GRK5. For this, Wistar female rats (~250g) were submitted to ovariectomy and on the following day they were treated with estradiol cypionate (10μg/rat, sc) or vehicle (corn oil, 0.1mL/rat, sc) for eight days. On the eighth day, the rats received an intracerebroventricular (icv, lateral ventricle) injection of angiotensin II (25ng/2μL/rat) or vehicle (0.9% saline, 2μL/rat). After five min of ANGII injection the animals were decapitated for brain collection for MKP-1 and GRK5 expression analysis by western blot. Data were analyzed using ANOVA two or three-way, followed by Newman-Keuls post-test and the level of significance was set at 5%. It was observed that E2 increased MKP-1 expression only in hypothalamus ($F_{1,18}$=24.3, $p<0.001$) in ovariectomized rats, independent of ANGII stimulus. Because the inhibitory effect of E2 on vasopressin release induced by ANGII was reversed by PKC inhibition, it was analyzed the role of PKC on MKP-1 expression and it was observed that PKC inhibition (Chelerythrine, 100μM/2μL/rat) reversed the positive effect of E2 on MKP-1 expression ($F_{1,30}$=4.7, $p<0.05$) in the hypothalamus. In addition, E2 decreased GRK5 expression only in the LT ($F_{1,21}$=12.7, $p<0.01$) in response to ANGII. Taken together, these results suggest that E2 requires PKC/MKP-1 pathway to decrease ERK1/2 phosphorylation in the hypothalamus and consequent vasopressin release induced by ANGII. While in the LT, the inhibitory effect of E2 involves decreasing GRK5 expression compromising ERK1/2 phosphorylation and sodium intake induced by ANGII. A significant contribution of this work is the identification of some steps of ANGII signaling modulated by E2, which can explain, at least in part, its regulation on the central ANGII effects.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Asymptomatic Severe Hypoglycemia with Lactic Acidosis in a Case of Non-Hodgkin's Lymphoma - an Unusual Phenomenon of Hyper-Warburgism

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INTRODUCTION

Hypoglycemia in malignancy is well known with several etiologies; impaired liver function, insulin receptor autoantibodies, production of insulin-like substance by malignant cells or large tumor burden. Another possible mechanism is the Warburg effect where metabolism shifts towards glycolytic pathways over oxidative phosphorylation even under aerobic conditions leading to excess lactate production. This leads to glucose consumption due to shunting of glucose away from normal cells to cancer cells. Very few cases of lactic acidosis and severe hypoglycemia in Non-Hodgkin's Lymphoma have been described in the literature. We report such an unusual case here.

CASE DISCUSSION

A 52-year-old, African-American male was admitted for severe malnutrition with 80 lb. weight loss, severe hypoglycemia and progressively increasing right chest wall mass. On arrival, he had no classic symptoms of hypoglycemia. Physical exam revealed persistent tachycardia, white patches on oral mucosa and posterior tongue, and an indurated mass on right chest wall with extensive swelling of right upper limb. Lab work was significant for blood glucose (BG) of 41 mg/dL (60–100), lactate 16 mmol/L (0.5 to 2), anion gap 26 mEq/L (3–10), albumin 2.3 g/dL (3.4 to 5.4) and normal renal and liver function tests. Fingerstick sugar readings were persistently in the 20s with no response to multiple boluses of dextrose and glucagon. He was started on dextrose 5% (D5) drip and intravenous solumedrol. Solumedrol was weaned off and D5 titrated down to investigate causes of hypoglycemia. BG dropped to 39 and corresponding labs showed insulin level of < 2 mcUnit/mL (2–20), C-peptide of 0.2 ng/mL (0.8–6.0) and ketone level of 0.2 mmol/L (<0.4). IGF-1 and IGF-2 were both low at 26 ng/mL (61–200) and 113 ng/mL (333–967) respectively. A CT torso with contrast showed bilateral pleural effusions, moderate pericardial effusions and a large ill-defined heterogeneous mass along anterior chest wall. He underwent ultrasound guided biopsy of the chest wall mass and diagnosed with diffuse large B-cell lymphoma. He also tested positive for HIV/AIDS and Hepatitis C. PET scan showed diffuse FDG (fluorodeoxyglucose) uptake consistent with advanced disease. He was started on chemotherapy and lactate and BG normalized soon after 1st cycle.

CONCLUSION

In our case; suppressed insulin, low C-peptide and IGF-2 levels indicate non-insulin mediated hypoglycemia due to rapid glucose utilization by cancer cells. Severe hypoglycemia with lack of neuroglycopenic symptoms suggests use of lactate (rather than glucose) as an alternative metabolic fuel for brain, thus preserving its function. Our patient presented with an exaggerated Warburg effect (hyper-Warburgism) as evident by extreme glucose consumption, severe lactic acidosis and large tumor burden on FDG/PET. Chemotherapy must be instituted timely to correct these abnormalities.