Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS I

Congenital Craniopharyngioma: A Rare and Challenging Disease

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Introduction: Congenital central nervous system tumors are seldomly seen, with just few reported cases of neonatal craniopharyngioma (NCP). Albeit being a benign tumor arising from epithelial vestiges along the adenohypophysis migration, NCP may have an aggressive behavior due to its location. Case Report: We report a two-month-old female infant referred to the Pediatric ward due to recurrent sepsis episodes, uncontrollable crying, large fontanelle and signs of adrenal insufficiency. Laboratory evaluation showed low serum cortisol 0.11 μg/dL (REF: 6.2-19.4 μg/dL), ACTH 6.66 pg/mL (REF: 7.2-63.3 pg/mL) and Na 133 mEq/L (REF: 7.2-63.3 pg/mL) and a slightly elevated prolactin 59.43 ng/dL (REF: 0.93-1.7 ng/dL) and a slightly elevated prolactin 59.43 ng/dL (REF: 0.93-1.7 ng/dL) and a slightly elevated prolactin 59.43 ng/dL (REF: 0.93-1.7 ng/dL). A transfontanelle ultrasound demonstrated a cystic and calcified sellar/suprasellar tumor. Encephalus Magnetic Resonance Imaging described a 36x42x33 mm multicystic sellar/suprasellar mass extending to the middle line and occupying all sellar space, leading to a deformed and compressed third ventricle, and displacing the mesencephalus, the cerebral pedunculus and the optic chiasm. Imaging evaluation suggested a craniopharyngioma. She started hydrocortisone therapy due to hypercortisolism and was submitted to transphenoidal surgery, but just a partial resection of the tumor was possible. She needed levothyroxine and desmopressin replacement after surgery. On the 10\(^{th}\) post-operative day she died due to infectious complications. The histological analysis of the tumor diagnosed an adamantinomatous-type grade I craniopharyngioma. Comments: Central nervous system tumors developing in the first 60 days of life are considered congenital. Besides being a rare condition, NCP are challenging and life-threatening. Although for some groups the complete resection of the tumor is considered the gold standard approach to those patients, sometimes it cannot be performed due to limitations intrinsic to the tumor biology and due to the patient’s age, worsening the prognosis of the infant. Multithoromonal deficits and shortened survival of this patient were consequences of the tumor characteristics, delayed diagnosis of craniopharyngioma and the poor results during and after the surgical intervention.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

Increased Risk of Bleeding and Excessive Anticoagulation Using Standard Dose Low Molecular Weight Heparin (LMWH) in Cushing’s Syndrome.

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Background: Cushing’s Syndrome (CS) is a hypercoagulable state with increased risk of venous thrombosis events (VTE) including pulmonary embolism (PE) and deep venous thrombosis (DVT). In the absence of clear recommendations (1), a standard dose of low molecular weight heparin (LMWH) is given: 1 mg/kg q12h (with dose reduction for CrCl < 30ml/min and low BMI). Here we report an excessive level of anticoagulation (based on standard LMWH anti-Xa levels) using standard dosing requirements in 8 of 11 patients with CS complicated by VTE who received treatment with Enoxaparin.

Methods: We retrospectively studied 6 women and 5 men with active hypercortisolism and VTE (6 PE and 5 DVT) treated with Enoxaparin given at doses below every 12 hours. Self-declared race/ethnicity were 7 white (one Hispanic), 2 unknown, 1 Asian, and 1 African. Anticoagulation therapy was monitored 4 hours after administration with measurement of LMWH anti-Xa (therapeutic range: 0.5-1.2 IU/mL). Results: The (subsequent) etiology of CS was ectopic ACTH secretion in 6 patients (5 pulmonary NET, 3 occult) and Cushing’s disease in 5. Median age was 53 years (range 24 - 74); median BMI 34.7 kg/M2 (range 24.9 - 52.9). Median urine cortisol was 659 mcg/24h (range 122 - 32,444; nl reference range 3.5 - 4.5). All had CrCl > 60 ml/min. 6 patients were taking a CYP3A4 inhibitor (Ketoconazole: n=5 or Mifepristone: n=1). 6/7 patients who received an initial dose of 1 mg/kg had supratherapeutic anti-Xa levels, from 1.4 - 2 IU/mL; five were on a CYP3A4 inhibitor. One died from a massive retroperitoneal bleed leading to organ failure. The other five required dose reduction; the median dose at which anti-Xa levels were at goal was 0.56 mg/kg (range 0.36 - 0.87 mg/kg). The sixth patient had an initial anti-Xa level of 0.2 IU/ml, which normalized on a dose of 1.1 mg/kg.

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One patient started at 1.3 mg/kg exhibited an anti-Xa level of 1.7 IU/ml, with appropriate anti-Xa levels at a dose of 0.6 mg/kg. 3 patients started at reduced treatment doses (0.68, 0.78 and 0.87 mg/kg) achieved therapeutic anti-Xa levels. In summary, therapeutic anti-Xa levels were achieved at a dose of approximately 1 mg/kg in only three patients (0.87, 0.96, 1.12 mg/kg); others required reduction of the usual recommended dose to between 0.36 and 0.78 mg/kg. CYP3A4 inhibitors were used in 5/8 patients with elevated anti-Xa levels.

Conclusions: Patients with Cushing’s syndrome appear to require lower than standard dose of enoxaparin; which may be only partly explained by concomitant CYP3A4 inhibitors. We suggest that anti-Xa levels be more closely monitored in CS patients to avoid morbidity and mortality caused by PE or bleeding. Further studies are needed to determine if this risk is present in patients receiving supraphysiologic doses of exogenous glucocorticoids.

1. Wagner J et al. Front Endocrinol (Lausanne). 9: 805, 2018

Neuroendocrinology and Pituitary
RESEARCH ADVANCES IN PITUITARY TUMORS

Pituitary Tumors and Immortalized Cell Lines Generated by Cre-Inducible Expression of SV40 T-Antigen
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Pituitary and hypothalamic cell lines have been developed by targeted oncogenesis. This involved using cell-specific transcrip- tional regulatory sequences to drive expression of large and small SV40 T-antigens in transgenic mice. Invariably, tumors develop in some of the mice, and the cells in these tumors can sometimes be adapted to grow in culture into stable, immortalized cell lines that maintain some of the features of differentiated cells. Cell lines that represent pre-gonadotropes (αT3-1), gonadotropes (L4T2), precursors to the POU1F1 lineage (GHT1, Pit1-zero), differentiated cells of the POU1F1 lineage (Pit1-triple, TaT1, and Pit1-PRL), and GnRH neurons (GT1-1) have been made by this approach. Tumors often develop early and cause infertility or death. To increase the opportunity for generating cell lines and to make it feasible to follow the process of tumorigenesis, we developed a mouse strain that expresses SV40 T-antigens in respond to cre-recombinase. Using CRISPR/Cas9 we inserted an 8 kb cassette with coding sequences for SV40 T-antigens and IRES-GFP into the Rosa26 locus, downstream from a stop sequence flanked by loxP sites: Rosa26<sup>LSL-SV40.GFP<sup>+</sup></sup>. 30% of the progeny born from hybrid zygotes injected with template DNA, CRISPR/Cas9, and sgRNA had correctly targeted the Rosa26 locus. These mice were mated with previously established Prop1-cre and Tshb-cre transgenic lines. The majority of Rosa26<sup>LSL-SV40.GFP<sup>+</sup> Prop1-cre and Rosa26<sup>LSL-SV40.GFP<sup>+</sup> Tshb-cre</sup> mice developed dwarfism and large tumors by 4 wks. The pituitaries of Rosa26<sup>LSL-SV40.GFP<sup>+</sup> Tshb-cre</sup> mice appear grossly normal at birth, but they are enlarged and showing evidence of increased vascularization by 2 wks. Flow-sorted GFP-positive cells from Rosa26<sup>LSL-SV40.GFP<sup>+</sup> Prop1-cre and Rosa26<sup>LSL-SV40.GFP<sup>+</sup> Tshb-cre</sup> mice express Prop1 and TSH, respectively. Tumors from Rosa26<sup>LSL-SV40.GFP<sup>+</sup> Tshb-cre</sup> mice were adapted to growth in cell culture. We have established a thyrotrope-like cell line that expresses Cga and POU1F1. These studies demonstrate the utility of the novel, Rosa26<sup>LSL-SV40.GFP<sup>+</sup> mouse line for reliable targeted oncogenesis and development of unique cell lines.

The authors have nothing to disclose.

Steroid Hormones and Receptors
STEREOID BIOLOGY AND ACTION

Salivary Cortisol and Cortisone Measurement Provide a Novel and Non-Invasive Method of Monitoring Medical Therapy in Cushing’s Syndrome
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