(subacute), depending on bleeding, edema extension, and necrotic evolution. It may result in severe neurological, ophthalmological, and endocrinological consequences and may require prompt surgical decompression.

**Case:** Our patient is a 17 year old AA tall male (Ht=86%) that was initially seen by neurosurgery with a history of progressive headaches over a period of 7-8 months, fatigue and abnormal brain MRI findings. He also reported sudden episodes of “blacking out” prompted by loud sounds. He did not have any visual complaints. He was referred to endocrinology and his work up showed hypopituitarism with a low baseline cortisol 5.1 ug/dL (6.2-19.4) with inappropriately normal ACTH 23 pg/ml (7.2-63.3), low free T4 0.72 ng/dL (0.93-1.6) with an inappropriately normal TSH 1.7 uIU/ml, low testosterone 18.4 ng/dL (350-970) without an elevated LH 1.1 mIU/ml or FSH 1.9 mIU/ml; low IGF1 74 ng/ml (153-542), normal IGFBP3 3316 ug/L (2657-6319); slightly elevated PRL 36.6 ng/ml (4-15.2). The initial brain MRI showed a pituitary mass, measuring 13x14x17 mm, which was homogenous with minimal upward lifting of the optic chiasm with concern for possible hemorrhage in the adenoma. He was started on maintenance and prn stress doses of hydrocortisone and subsequently thyroid hormone and testosterone gel with improvement of symptoms. A repeat MRI approx. 3 months after showed no interval change. Decision was made to proceed with endoscopic transphenoidal hypophysectomy. There were no complications, (i.e., DI). The pathology report described “organizing hematoma and fragments of sinus mucosa.” He had labs repeated nearly 4 weeks post op with an improvement in his IGF 1 211ng/ml (151-521), and PRL 12 ng/ml (3-18). His FT4 after thyroid hormone implementation was 1.64 ng/dl (0.93-1.6). His testosterone was slightly lower than in the initial one (testosterone 161.8 ng/dl) but he was less compliant with testosterone therapy.

**Conclusion:** Pituitary apoplexy is rare in the pediatric or adolescent population and is restricted to case reports. It remains a diagnostic and therapeutic challenge and specific guidelines are lacking. The outcome is highly variable and the optimal time of surgery is still a matter of debate. For our patient serial imaging will show if there is recurrence of a lesion and repeated pituitary function will allow us to determine need for hormone replacement over time since resolution of existing deficiencies or development of new ones have been reported.

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**Thyroid**

**THYROID NEOPLASIA AND CANCER**

**Detection of RAS Mutations and RET/PTC Fusions in Thyroid Cancer Using Microfluidic Digital PCR**

**SUN-907**

**MON-514**

**Detection of RAS mutations and RET/PTC fusions in thyroid cancer using microfluidic digital PCR**

**Background:**

The identification of somatic mutations and gene fusions is crucial for guiding therapeutic decisions in patients with thyroid cancer. Microfluidic digital PCR is currently considered as a technique of choice for highly sensitive detection of gene mutations/fusion. We recently demonstrated that dPCR is a useful tool for detection of BRAFV600E and TERT promoter mutations in thyroid tumors.

**Objectives:**

This study aimed to determine the analytic and clinical validity of dPCR for detection of RAS mutations and RET/PTC fusions in thyroid cancer tissue.

**Material and Methods:**

Thyroid tissues from 75 patients with PTCs (58 classical PTC (CPTC) and 17 follicular variant (FVPTC)) were used for DNA and RNA extraction. The rare mutation SNP genotyping assays which were multiplexed for detection of mutant and wild type NRASQ61; as well as RET/PTC1 and RET/PTC3 were synthesized by Thermo Fisher Scientific. Digital PCR was performed using a QuantStudio 3D Digital PCR platform. QuantStudio Software was used for relative and quantitative data analysis.

**Results:**

NRASQ61 was detected in 0/58 CPTC and in 6/17 (35%) FVPTC. The ratios of mutant/total varying from 11.7% to 61.5%. Among patients with FVPTC there were no significant associations between the presence of NRASQ61 and patient's age, sex, multifocal growth, extra-thyroidal invasion and lymph node metastases. The ratios mutant/total correlated with tumor size in patients harboring NRASQ61. In 23 cases, RET/PTC1 and RET/PTC3 transcripts were examined. RET/PTC1 and RET/PTC3 transcripts were detected in 3 and 1 case, respectively. RET/PTCs were detected in CPTC, but not in FVPTC. RET/PTC positive tumors were characterized by multi-focal patterns of growth, presence of extra-thyroidal invasion, and presence of lymph node metastases (4 of 4 cases with RET/PTC). There were not RET/PTCs positive tumors harboring simultaneously anomalies in RAS oncogene.

**Conclusions:**

Microfluidic digital PCR allows specific, sensitive and rapid detection of RAS mutations and RET/PTC fusions in thyroid tissue samples. Implementation of dPCR-based assays may facilitate analysis of thyroid tumors and support research in patients with thyroid cancer.

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**Tumor Biology**

**ENDOCRINE NEOPLASIA CASE REPORTS I**

**Dual Ectopic Gastrin and ACTH Secretion Leading to Combined Zollinger-Ellison Syndrome and Cushing’s Syndrome in a Patient with Metastatic Neuroendocrine Pancreatic Tumor**

**Leigh Kwek, MD, Julia Caroline Wingate Lake, MD, Simrun Bal, MD, Andrew Robert Crawford, MD, Sushela S. Chaidaran, MD, PhD, FACE, FACP**

Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA.

**SUN-907**

**Background:**

Zollinger-Ellison Syndrome (ZES) is caused by ectopic secretion of gastrin from a gastrinoma. The annual
incidence of gastrinomas is 0.5 to 2 per million population\(^1\). Although 17-30\% of gastrinomas will stain positive for both gastrin and ACTH, the clinical manifestation of both ZES and Cushing’s syndrome is rare. In a study by Maton et al., 3 of 59 patients (5\%) with sporadic ZES (not MEN1) had Cushing’s syndrome as well\(^2\).

Clinical Case:
A 63yo woman with DM2 presented with persistent diarrhea for 2 years, and was diagnosed with ZES with a gastrin level of 1359 pg/mL (<100 pg/mL). A CT A/P showed a 3.8 cm pancreatic tail mass with multiple liver lesions. These lesions showed positive uptake on octreoscan, and a biopsy was positive a pancreatic neuroendocrine (NE) tumor. Her diarrhea was controlled with a PPI and no other intervention was made.

7 months later, she experienced severe worsening of her DM control despite aggressive medication titration. Due to new confusion and lethargy, she presented acutely to the ED. Labs showed metabolic alkalosis and profound hypokalemia with a CO\(_2\) 38 mmol/L (22 - 31 mmol/L), venous pH 7.58 (7.32 - 7.42) and K 2.1 mmol/L (3.5 – 5.0 mmol/L). Her skin was diffusely hyperpigmented, and she had numerous cushingoid features on exam including supraclavicular fat pads, round face, thin skin and thin extremities. A subsequent cortisol level was found to be 125 mcg/dL (AM [6-10 am] 4.8 – 19.5 mcg/dL) with an ACTH of 1081 pg/mL (6-50 pg/mL).

She was not an optimal candidate for adrenalectomy given previous abdominal surgeries. After an octreotide drip (total 1475 mcg in 24 hrs) failed to reduce cortisol levels, metyrapone 250 mg q6h was started which led to an immediate and significant reduction in cortisol levels, metyrapone 250 mcg q6h was started which led to an immediate and significant reduction in cortisol (209 to 38 mcg/dL), improved quality of life and significant reduction in her insulin and K supplementation requirement.

Conclusion:
We present a rare case of a dual gastrin and ACTH-secreting metastatic pancreatic NE cancer, in which overt ZES preceded the relatively abrupt onset of clinical Cushing’s syndrome. Similar to Babu et al., the initial presentation was dominated by worsening DM control\(^3\). Despite the octreoscan positivity, cortisol production was not appreciably blocked by octreotide but was well controlled by metyrapone.

As seen in other cases, we again highlight the pluripotency of NE tumors and the ability to change hormone production. We also present the unique circumstance this patient faced for treatment options as she was not an optimal candidate for surgery.

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**Neuroendocrinology and Pituitary**

**ADVANCES IN NEUROENDOCRINOLOGY**

**Protein Induced Pancreatic Hormone Secretion Is Modulated by Vagal CaSR**

Mariana Norton, PhD\(^1\), Simon C. Cork, PhD\(^1\), Aldara Martin Alonso, MSc\(^2\), Anna G. Roberts, MSci\(^3\), Yateen S. Patel, MRes\(^1\), Siying Cheng, MRes\(^1\), Robert Hansford, BSc\(^1\), Ye Cao, MRes\(^1\), Victoria Salem, MBBS\(^1\), Aylin Carla Hanyaloglu, PhD\(^1\), Wenhan Chang, PhD\(^2\), Kevin Graeme Murphy, PhD\(^1\).

\(^1\)Imperial College School of Medicine, London, United Kingdom,  
\(^2\)UCLA, San Francisco, CA, USA.

**SUN-266**

The existence of a vago-vagal entero-pancreatic pathway, where sensory information from the gut can signal via vagal afferents to the brain to mediate changes in pancreatic function, has been recognised for over a century, and investigated extensively with regards to pancreatic exocrine secretions. However, the role of such pathways in pancreatic endocrine secretions has received less attention.

The secretion of insulin and glucagon in response to protein and amino acids is conserved across species. This effect is thought to promote amino acid uptake into tissues without concomitant hypoglycaemia. We found that the essential amino acid L-Phenylalanine potently stimulates glucagon secretion, even when administered directly into the gut at small doses unlikely to significantly raise systematic levels.

Administration of L-Phenylalanine also increased neuronal activation in the rat and mouse dorsal vagal complex, the central nervous system region directly innervated by vagal afferents.

L-Phenylalanine modulates the activity of the calcium sensing receptor (CaSR), a nutrient sensor more commonly known for its role in calcium homeostasis, but which is thought to also act as a sensor of aromatic amino acids. Interestingly, the CaSR is one of the few nutrient sensors expressed in vagal afferents and in vitro calcium imaging revealed CaSR synthetic agonists activate subpopulations of vagal afferents.

The role of CaSR in vivo was investigated further by selectively knocking down the CaSR in vagal afferents. Briefly, CaSR floxed mice were bilaterally injected directly into the nodose ganglion, where the cell bodies of vagal afferents are located, with a cre expressing adenovirus. CaSR knockdown did not interfere with normal food intake, nor the vagal-dependent anorectic effects of cholecystokinin, or of L-Phenylalanine. However, it did blunt protein-induced glucagon secretion, suggesting involvement of the CaSR in the vagus nerve in protein sensing and glucose homeostasis.

Future studies are required to determine the importance of vagal CaSR in protein induced pancreatic endocrine secretions, and the possibility of exploiting this circuit to develop new anti-diabetic therapies.