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MON-453

Introduction: Papillary thyroid cancer (PTC) is the most common thyroid tumor in childhood. Most patients are referred with locally advanced and/or distant disease at the time of diagnosis. Whenever possible, these patients should be offered total thyroidectomy and radioiodine remnant ablation; however, this approach is not always feasible, rendering these tumors unresectable. These critical cases could benefit from neoadjuvant treatment with multikinase inhibitors (MKI) so that standard treatment can be performed. Lenvatinib is an MKI recently approved in many countries throughout the world for the treatment of radioiodine refractory adult differentiated thyroid cancer. Only few pediatric cases have been reported. Case report: A 10-year-old female patient with locally advanced PTC and metastasis to the lungs, who required 3 liters of oxygen due to respiratory failure caused by bilateral miliary lung disease, mistakenly treated as tuberculosis two months previously and referred to our Hospital. A large thyroid mass adhered to deep tissues was confirmed on CT scan, showing a large heterogeneous neck mass with multiple microcalcifications associated with multiple lymph nodes. Both lungs had multiple micro-nodular disease with interstitial involvement. Total thyroidectomy together with lymph-node dissection was planned, but extensive local infiltration made the lesion unresectable and surgery was limited to a thyroid biopsy. The patient required respiratory assistance. Histopathology confirmed the presence of a PTC (diffuse sclerosing variant) with a *RET-PTC3* oncogene rearrangement. Eight days after surgery the patient was critical and we decided to indicate the compassionate use of Lenvatinib. The patient was started on oral lenvatinib at a dose of 14 mg daily (14 mg/m/day). Three days later, she clinically improved and nine days post-lenvatinib initiation, the patient was discharged from hospital without need for oxygen therapy. Lab studies showed a rise in thyroglobulin levels in the first month of treatment followed by a significant drop. All Lung Function Test parameters significantly improved. The patient initially had severe restrictive breathing and due to the resting dyspnea with hypoxemia she could not perform the walking test. Two months after treatment onset she could walk 360 meters in six minutes with 96% oxygen saturation. After 4 months on Lenvatinib, imaging studies showed a stable thyroid mass while the pulmonary nodules appeared stable to slightly smaller without evidence of new or progressive disease. Conclusion: On lenvatinib treatment, our patient showed significant clinical improvement, arrest of disease progression, and stable disease on imaging studies. This case shows that lenvatinib may be a beneficial option for children with advanced PTC not amenable to surgery/RAI treatment and may be used as a bridge to these first-line therapies.

Pediatric Endocrinology

PEDIATRIC GROWTH AND ADRENAL DISORDERS

Identifying Distinct Facial Dysmorphology in Youth with Congenital Adrenal Hyperplasia Using Deep Learning Techniques

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Purpose: Classical Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency affects 1:15,000 newborns and involves adrenal insufficiency and androgen excess. These hormone abnormalities are evident as early as 7 weeks' gestation and persist throughout pregnancy. Structural brain abnormalities are also known to occur in CAH, with abnormalities of brain and facial structure occurring together in conditions such as fetal alcohol spectrum disorder and holoprosencephaly. As well, sex differences in facial morphology are well described in healthy individuals. Thus, we aimed to study facial features using artificial intelligence in CAH youth. **Methods:** We studied frontal images of the face in 57 youth with severe salt-wasting CAH (60% female; 9.4±5.5y), and 38 controls (47% female, 9.7±5.1y), acquired with an iPad v12.1. We included 32 additional controls (43% female; 4-19y) from a publicly available face image dataset (1). Applying deep learning techniques, we converted 2-D facial photos to mathematical descriptors in order to differentiate features between groups. For a given test image, our pipeline output was a predicted "CAH score" between [0,1]. Due to our small dataset, we employed K-fold cross validation to train and test our deep neural network. At each of the K-9 folds, 88% of data (468 control and 531 CAH images) were used to train the network, with the remaining data (55 control and 63 CAH images) used to test the trained network. Test results were validated in terms of area under the curve (AUC) of receiver operating characteristic curves (generated from predicted CAH scores of test subjects), to analyze true and false positive rates. Our pipeline automatically detected face-bounding boxes and 68 facial landmarks (dlib toolkit) which were then used to compute 27 Euclidean (linear) facial features (2,3). We performed between group analyses of features with t-tests. **Results:** The averaged AUC of nine folds was 0.83±0.14, representing strong predictive power as a proxy to correlating facial dysmorphology with CAH. Predicted CAH scores were different between control (0.24±0.33) and CAH (0.69±0.37; $p<0.0001$) youth. Thirteen of 27 facial features were different between controls and CAH ($p<0.05$ for all) including 3 of 6 features related to sexual dimorphism. We also produced heat (i.e., saliency) maps showing the effect of CAH on facial features, and 2D t-SNE plot visualization of features showing well-defined separation between CAH and control group clusters. **Conclusions:** Utilizing deep learning, we have shown that CAH youth have facial features that can reliably distinguish them from controls. Further study is merited in regard to the etiology of affected facial morphology in CAH, and associations with

disease severity, and/or brain and behavior abnormalities. (1) Masi I et al. Int J Comput Vis 2019. (2) Whitehouse AJ et al. Proc Biol Sci 2015. (3) Lefevre CE et al. Evol Hum Behav 2013

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Spiral Steroid Lactones Are Synthesized by Condensation of a Steroid Precursor with Coenzyme a Derivatives

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Background: Szent-Gyorgyi proposed that digoxin wasn't really drug but was a substitute for an endogenous cardiotonic steroid (ECS). Endogenous ouabain and marinobufagenin have been proposed as ECS.

Hypothesis: Ionotropin, our first candidate for the ECS, is unique among steroids because it is the phosphocholine ester of a steroid with 23 carbon atoms. Logically, either there must be a novel mechanism for adding carbon atoms to a pregnenolone-like precursor or a novel mechanism for side-chain cleavage from a cholesterol-like precursor.

Experimental design: Serum samples were extracted with acetonitrile, filtered and analyzed by MS-^{N} on an LTQ-XL ion trap mass spectrometer. The instrument permits multiple rounds of fragmentation and identification of the parent ion and each fragment ion. This process permitted recognition of ions that were phosphocholine esters and of the mass of the steroid fragments. The chemical formula of each steroid fragment was determined by trial and error analysis. Although not every mass ion has a unique chemical formula, in fact, each of the steroid ions had a unique formula. Possible isomers were resolved by consideration of knowledge of steroid biosynthetic pathways.

Major results: In brief, human serum samples had steroid fragment ions consistent with 23 (354 Da) and 25 (398 Da) carbon atoms. This provides an additional constraint as the synthetic mechanism must account for both products. These mass ions were consistent with condensation of either acetyl-CoA or acetoacetyl-CoA with the phosphocholine ester of pregna-5,7-diene-3β,17α-diol-20-one. After condensation, the steroid adduct would be dehydrated and cyclized to form the corresponding spiral steroid phosphocholine ester. This pathway is similar to the mechanism of addition of 2 carbon fragments to a long chain fatty acid. This is the first explanation for the biosynthesis of endogenous mammalian ECS. Spiral lactones would be expected to cross react with many antibodies specific for digoxin, ouabain or marinobufagenin. Either one of the spiral lactones would satisfy Szent-Gyorgyi's suggestion as the endogenous digoxin-like material.

Conclusions: In summary, we have isolated 2 spiral steroid lactones from mammals and identified the mechanism of their biosynthesis. We propose, as the spiral steroids share structural features with the spironolactone class of potassium sparing diuretics, that they also share functions. Nicholls proposed that a candidate for ECS should not be accepted without [a] isolation, [b] precursors, and [c] a biosynthetic path. As there has been no satisfaction of these requirements for ouabain or marinobufagenin, their existence as ECS in mammals needs to be reconsidered.

Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

The Effect of Leptin Treatment on Blood Pressure and Autonomic Nervous System Function in Patients with Lipodystrophy.

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SUN-565

Leptin is an adipokine that reflects energy storage levels. Patients with obesity have high leptin, hypertension, and increased cardiovascular disease (CVD) risk. In rodents, leptin increases blood pressure (BP), by increasing sympathetic nervous system (SNS) activity, suggesting high leptin may cause hypertension and CVD. Studies of leptin administration in 2 human models of leptin deficiency (weight reduced and congenital leptin deficiency) showed decreased SNS activity in the leptin-deficient state, which increased after leptin replacement. This has clinical relevance as high SNS and low parasympathetic nervous system (PNS) activity correlate with increased risk of hypertension and CVD. In lipodystrophy syndromes adipose tissue is deficient thus leptin is low. We hypothesized that leptin treatment in patients with lipodystrophy would increase SNS activity and BP. SNS and PNS activity in the heart can be assessed using heart rate variability (HRV). The high frequency (HF) component of HRV is directly related to PNS activity whereas the low frequency (LF) component reflects both SNS and PNS. The LF/HF ratio reflects sympathetic-vagal balance. Lower standard deviation of the beat to beat interval (SDNN) inversely correlates with CVD risk. Leptin-naïve patients with lipodystrophy (N=17, 5 generalized, 12 partial) were housed on an inpatient unit for 19 days. Patients were studied without leptin for the first five days. Leptin was administered for the next 14 days. At the end of the OFF-leptin and ON-leptin periods, 24-hr EKG recordings were used to derive HRV parameters and an automated BP monitor measured BP every 30 minutes during the day and every 60 minutes at night. 5 patients had generalized lipodystrophy (median 25^{th},75^{th} percentile] endogenous leptin [0.5 [0.4, 0.6] ng/mL); 12 had partial lipodystrophy (leptin 7.5 [3.9, 20.3]). In the combined cohort with generalized and partial lipodystrophy, leptin treatment did not alter BP or any measure of autonomic nervous system function after 24 hours, 2 weeks, or 6 months. In exploratory subgroup analyses of generalized vs partial lipodystrophy, those with generalized lipodystrophy had an increase in LF after 2 weeks of leptin and a 4.5 mm Hg increase in systolic BP after 6 months; no changes were observed in those with partial lipodystrophy. Unlike previous human and rodent studies, we did not see increased SNS tone or BP after leptin treatment in patients with lipodystrophy. However, exploratory analyses in patients with generalized lipodystrophy and very low endogenous leptin