Flávia Rezende Tinano, MD, Berenice Bilharinho Mendonca, MD, PhD, Ana Claudia Latronico, MD, PhD, Vinicius Nahiime Brito, MD, PhD.  
Unidade de Endocrinologia do Desenvolvimento, Laboratório de Hormônio e Genética e Molecular/LIM 42, Hospital das Clínicas, Disciplina de Endocrinologia e Metabologia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, São Paulo, Brazil.

SUN-061
Ovarian estrogen-secreting cysts leading to peripheral precocious puberty (PPP) are some of the major clinical manifestations of the McCune-Albright syndrome (MAS). Therapeutic options for PPP of MAS include tamoxifen, progestational agents, aromatase inhibitors (AI) and anti-androgens that aiming to block sex steroid synthesis or action. Here, we described the anthropometric and reproductive follow-up of patients with PPP of MAS treated with distinct therapeutic agents. Thirteen unrelated girls with MAS were studied. They had PPP combined with café-au-lait spots or/and fibrous dysplasia. All patients were treated with one or more of the following agents: tamoxifen, medroxyprogesterone acetate, aromatase inhibitors (anastrozole or letrozole) and anti-androgens (cyproterone), and, in cases with secondary gonadotropin axis activation, depot GnRHa was used. Patients were evaluated every three months, when height, weight, and Tanner pubertal stage were determined. Vaginal bleeding or other adverse effects were also reviewed. The chronological age (CA) at the diagnosis of PPP was 5.9 ± 2.35 (2.4 to 10.2 years). Thelarche and vaginal bleeding were the first manifestations in 78.9% and 53%, respectively. The first choice of treatment was tamoxifen in 30.7% of the patients, followed by aromatase inhibitors (23%) and medroxyprogesterone acetate in 23% of them. Tamoxifen plus medroxyprogesterone, or cyproterone, or leuprorelin were used (each one) as the first choice in 1 patient (7.6%). Eight patients (61%) presented secondary central precocious puberty and were treated with depot GnRHa. Vaginal bleeding was recurrent in 70% of patients, during treatment. Progression of breast Tanner stage during treatment occurred in 78% of the patients. The great majority (80%) of girls presented bone age (BA) advancement at the diagnosis of PPP (mean Δ BA - CA of 3.2±1.3 yr), which was normalized for chronological age in all except one patient. The mean duration of treatment was 5.8 ± 3.4 yr (ranging from 1 to 12 yr). Three patients are still under medical treatment. Hypertrichosis and uterine enlargement were the main side effects of tamoxifen in 3 and 5 patients, respectively. One patient treated with letrozole presented laboratory hyperandrogenism. Ten patients reached their adult height (149.9 ± 7.9 cm), 60% of them were below their target height. Menarche occurred at a median age of 11.8 yr (10.4 to 14 y), and all but one patient presented regular menstrual cycles. One patient spontaneously became pregnant. Despite a reasonable number of treatment options for peripheral PP in MAS, none of them showed proven effective results in stopping vaginal bleeding, reduce pubertal progression and preserving potential genetic adult height. Therefore, due to the extremely heterogeneous nature of PPP of MAS, the clinical treatment remains a challenge.

Pediatric Endocrinology

PEDiatric PUBERTY, TRANSgendEnrHEALTh, AND general eNdOCRINE

Long Term Outcomes in Patients with Disorders of Sex Development in Lucknow, North India
Vijayalakshmi Bhattri, MD,MBBS, Nibu Dominc, MD, DM. Sanjay Gandhi Inst of Med Sci, Lucknow, India.

SUN-056
Due to the deviant genitalia and infertility, the ill effects of DSD are on sexual and psychosocial life. Our aim was to assess the self-reported psychosocial and sexual quality of life in older individuals who are living with a DSD. Quality of life in 31 patients with a DSD (age >16 years, median [IQR] 23 [19-27] years, 16 males) was compared with age, sex and socioeconomic status matched normal (n = 46) and chronic disease controls (type 1 diabetes patients, n = 43) using SF-36v2 Health Survey. Another structured questionnaire was administered touching upon domains of sexual and psychosocial life. Eighteen patients reported history of persistent teasing, with no difference in prevalence between males and females. Eighteen reported suicidal thoughts (no association with being teased), 6 having attempted suicide. Gender identity (GI) of 30 patients was identical with their given sex of rearing, which had been decided by the caregiver in 19 families (including one who had gender change suggested by the parents at 4 years of age), and with physician assistance in 11. One patient had spontaneous change of GI at 16 years age. Sexual orientation was heterosexual in 25 of 29 who responded to this question, homosexual in 1 and bisexual in 3, including the 2 who had gender change. Romantic relationship was reported by 12 patients, sexual activity by 7, aversion to sex (due to fear of rejection) by 11 and abuse by 4. Seventeen patients thought the timing of genital surgery should be before age 5 years and another 10 before age 10 years. Only 2 of 31 patients thought decision for the timing and choice of surgery should rest with themselves, the remainder preferring a decision by parents in 25% and by the physician in 67%. The physical and mental quality of life scores (QOLS) were not different between patients and the controls. Mental QOLS were significantly lower for those with history of teasing. Physical QOLS in males correlated with external masculinisation score (r=0.55, p=0.04). Conclusion: Serious psychological stress is common in patients with DSD in our region. Despite early sex assignment, the absence of prominent gender dysphoria in adulthood, along with their stated preference for corrective genital surgery at an early age, favour an early sex assignment and genital reconstruction before the age of romantic relationships.

Thyroid

THYROID DISORDERS CASE REPORTS III

Coexistence of Thyroid Dysgenesis and Premature Ovarian Failure: A Case Report
Catherine P. Calma, MD, May U. Naranjo, MD, Valerie U. Lima, MD, Jeannine Erika M. Tarongoy, MD. Davao Doctors Hospital, Davao City, Philippines.

MON-474
Co-existence of Thyroid Dysgenesis and Premature Ovarian Failure: A Case Report
Background. Congenital hypothyroidism (CH) secondary to thyroid dysgenesis is rare. It may present with ascites and short stature. Primary ovarian failure (POF) is most commonly associated with autoimmune thyroid diseases. However, there is no report of the association of POF with congenital hypothyroidism.

Clinical case. A 30-year-old female presented with increasing abdominal girth, short stature and arrest of menstruation at 27 years old. Newborn screening was not done. Developmental milestones were at par. She had a low timber voice and was slow to respond. Her skin was rough and dry. Her hair was sparse, and she had thin eyebrows. Her tongue was not enlarged. Her abdomen was globular with a positive fluid wave test and shifting dullness. Initial tests indicated a hypothyroid state: elevated TSH (50.40 IU/mL, N=0.35-4.94 IU/mL), low FT4 (0 pmol/L, N=12-22 pmol/L). Ultrasound of the thyroid suggests thyroid dysgenesis (small right thyroid gland measuring 1.4 x 0.2 x 0.4 cm and an absent left thyroid gland). Karyotyping was 46, XX and insulin growth factor 1 was normal. Unexpectedly, further tests were consistent with a concomitant primary ovarian failure: low estradiol (5 pg/mL, N=12.4-233 pg/mL), high FSH (112.7 mIU/mL, N=3.5-12.5 mIU/mL) and LH (61.9 mIU/mL, N=2.4-12.6 mIU/mL). Chest radiography showed left pleural effusion. Abdominal CT scan showed marked ascites with normal reproductive organs. Anti-TPO antibodies were normal (4.87 IU/mL, N=0-25 IU/mL). The patient was treated with Levothyroxine 50 mcg daily then gradually increased to 100 mcg daily. She was given Spironolactone 50 mg daily.

Conclusion. This case report emphasizes the importance of the early detection of congenital hypothyroidism through newborn screening. Severe hypothyroidism is rarely seen due to the wide availability of the TSH assay and its diagnosis should instigate further work-up for its etiology. Concomitant premature ovarian failure in the absence of an autoimmune thyroid disorder should prompt further investigation for another etiology since premature ovarian failure is not commonly associated with congenital hypothyroidism.

Reference: (1) Ayesha, Jha V, Goswami D. Premature Ovarian Failure: An Association with Autoimmune Diseases. J Clin Diagn Res. 2016;10(10):QC10-QC12.

Genetics and Development (including Gene Regulation)

Genetics and Development and Non-steroid Hormone Signaling I

SG-2 as Novel Multi-Target Directed Ligand (MTDL) for the Treatment of Neurodegenerative Diseases (NDDS)

Simona Sestito, PhD1, Massimiliano Runfola, PhD1
Lavinia Bandini, Dr1, Filippo Santucci, MD1, Nicola Origlia, PhD1, Simona Rapposelli, PhD1, Grazia Chiellini, PhD1
1University of Pisa, Italy. doi: 10.1210/jendso/bvaa046 | Journal of the Endocrine Society | A875

Thyroid

THYROID DISORDERS CASE REPORTS II

A Case of Pituitary Hyperplasia Secondary to Uncontrolled Primary Hypothyroidism

Hebah Alhumaidi, B.M.B.Ch.1, Sarika Rao, DO2, Dhruv Kansal, M.B.B.S3
1Mayo Clinic, Jacksonville, FL, USA, 2Maulana Azad Medical College, New Delhi, India.

SUN-717

NDDs are progressive multifactorial disorders that impair memory, cognition, movements, and general functioning. This deterioration is mostly due to inflammation triggered by aberrant protein deposition, oxidative stress and modification in lipid pathways. Because of these multifactorial aspects, the development of multi-target directed ligand (MTDL) could represent a potential strategy for the treatment of NDDs.

Recently, the thyronamine-like analog SG-2, originally developed as a synthetic TAAR1 agonist, has revealed to efficiently reprogram lipid metabolism and to produce memory-enhancement in mice. Long-term potentiation (LTP) is one of the basic mechanisms of memory. LTP is inhibited by beta-Amyloid oligomers (Aβ), and in the early stage of AD it is selectively impaired in the entorhinal cortex (EC).

In the present study, to further expand our knowledge on the potential of this novel analog to act as a neuroprotective agent, we investigated if administration of SG-2 has any effect on LTP in EC of a transgenic model of AD (hAPP-J20 mouse).

Extracellular in vitro recordings were performed in EC slices from 2-month-old APP-J20 mice: field potentials were evoked in layer II after stimulation of the same layer and LTP was elicited by high frequency stimulation (HFS), consisting of three trains of 100 pulses at 100 Hz. SG-2 (1 or 5 μM) was administered for 10 minutes, starting 5 minutes before the delivery of HFS.

LTP cannot be elicited by HFS in mhAPP slices perfused with artificial cerebrospinal fluid (ACSF) alone. When we tried to rescue LTP in mhAPP slices using SG2 at the lowest concentration (1 μM), 10 min perfusion with SG2 was not effective. In contrast, a higher concentration of SG2 (5 μM), rescued LTP to a level that was significantly higher than that observed in mhAPP slices alone (n=6; p=0.046), as well as in mhAPP slices perfused with SG2 1 μM (n=5; p=0.043). Our results suggest that SG-2 plays a neuroprotective effect, rescuing Aβ-induced neuronal dysfunction and might open new perspective in the study of AD.

Metabolic reprogramming and neuroprotective functions for the histone deacetylase SIRT6 are well known, and a reduction of SIRT6 expression has been observed in patients with AD. Exposure of human neuroblastoma (SH-SY5Y) cells to SG-2 (1 or 10 μM) resulted in significant (p<0.044) over-expression of SIRT6, and concomitant activation of AMPK leading to the inhibition of mTOR phosphorylation, further underlying potential for SG-2 as a multi-target neuroprotective ligand.

Reference: (1) Belluscio et al. Frontiers in Pharmacology 2017; 8: 905.