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[1]. 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 and paracentesis was also done to address ascites. The patient had improvement of symptoms after a month of treatment. However, the etiology of POF remains to be further elucidated.

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

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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[1]. 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 (1μM), 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) Bellusci et al. Frontiers in Pharmacology 2017; 8: 905.

Thyroid

THYROID DISORDERS CASE REPORTS II

A Case of Pituitary Hyperplasia Secondary to Uncontrolled Primary Hypothyroidism

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