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GENETIC

56622 APPLICATION OF TARGETED NEXT GENERATION SEQUENCING TO THE MOLECULAR DIAGNOSTICS OF CONGENITAL HYPOTHYROIDISM

Frédérique Savagner[1], Virginie Jacques[1], Manon Cassou[1], Malvina Signorino[1], Graciela Testa[1], Mirta Miras[1], Paula Scaglia[1], Horacio Domene[1], Patricia Papendieck[1], Ana Chiesa[1], Juan Pablo Nicola[1]

[1] Universidad Nacional del Córdoba

Introduction: Congenital hypothyroidism is the most frequent endocrine disorder in pediatric patients with an incidence of 1:2,000-4,000 newborns. Thirty monogenic forms of congenital hypothyroidism have been reported in individuals with congenital hypothyroidism, highlighting the genetic heterogeneity of the disease. **Objective:** A meta-analysis demonstrated that only 5%-10% of patients with thyroid dysgenesis and 45%-88% of patients with thyroid dyshormonogenesis are diagnosed using single-gene sequencing. Here, we used targeted next generation sequencing approach to investigate the etiology of congenital hypothyroidism. **Material and methods:** Genomic DNA from 13 pediatric patients with permanent congenital hypothyroidism due to thyroid dysgenesis (n = 2) or dyshormonogenesis (n = 11) was explored by targeted next generation sequencing to analyze the coding sequence of 17 candidate genes (TG, TPO, DUOXA2, DUOX2, SLC5A5, SLC16A2, SLC26A4, TSHR, GNAS1, THRB, THRA, PAX8, NKX2.1, NKX2.5, FOXE1, IYD, SECISBP2) involved in the pathogenesis of congenital hypothyroidism. **Results and conclusions:** Among all 13 patients studied, 7 (54%) presented simple or compound heterozygous variants in genes involved in thyroid organogenesis or hormonogenesis. No homozygous variants or small gene deletion/insertions were evidenced. One patient with thyroid dysgenesis showed a heterozygous FOXE1 variant (p.P203R). In addition, one patient with thyroid dyshormonogenesis showed compound heterozygous TG variants (p.D29X; c.177-2A>C). The remaining patients with thyroid dyshormonogenesis showed simple heterozygous TG (p.F1542Vfs*20; p.T2563C; p.S523P) or DUOX2 (p.E1496Dfs*51; p.W178L) variants. All identified variants were predicted pathogenic or reported as pathogenic in the literature. Of note, none of the 13 patients under study presented variations in more than one gene involved in thyroid hormonogenesis. Surprisingly, most of the patients evidenced a significantly loose correlation between clinical phenotype and genotype. Targeted next-generation sequencing constitutes an attractive alternative to systematically explore and diagnose congenital hypothyroidism. However, we evidenced that a considerable proportion of patients (46%) remain undiagnosed. Further molecular analysis, such as whole-exome sequencing, may provide novel insights into the pathogenesis of congenital hypothyroidism.

IODINE DEFICIENCY

56706 UNRECOGNIZED TRANSIENT HYPOTHYROIDISM DUE TO IODINE DEFICIENCY IN NEWBORNS RECEIVING TOTAL PARENTERAL NUTRITION: HOW COMMON IS IT?

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Iodine is critical for thyroid hormones synthesis, normal growth and neurological development in children. Iodine deficiency (ID) was a common cause of hypothyroidism in Brazil; nowadays it's a rare condition due to supplementation in cooking salt. Premature newborns are more vulnerable to iodine deficiency and must receive 90 mcg/day of elemental iodine, according to WHO. Today there is no formal recommendation for iodine use in total parenteral nutrition (TPN) in Brazil. We report a case of a 2-month old female patient born at 26 weeks gestation due to eclampsia. Right after birth, she presented respiratory distress syndrome. TPN was initiated on the first day because of very low birth weight. Thyroid function was assessed to investigate constipation, which reveals TSH 18 mUI/ml and free T4 0.95 mcg/dL (normal range 3.8 ± 4.7 mUI/ml and 1.5 ± 0.4 mcg/dL) suggestive of primary hypothyroidism. However, the neonatal screening test collected at 5th day of life was normal (TSH 2.7 mUI/ml), leading to other hypotheses to explain the case. We revised TPN nutrient composition prepared in our Institution and observed that there was no iodide, raising the hypothesis of transient hypothyroidism due to ID. We started reposition with Lugol 2% (iodine 650 mcg/weekly), at oral mucosa. Tests performed 15 days later were normal (TSH 1.72 mUI/ml, free T4 1.99 mcg/dL). Enteral nutrition was initiated after 2 days and was well tolerated, making it possible to suspend TPN and iodine replacement 4 days later. The TSH measurement one-week later was 4.03 mUI/ml. She had multiple clinical intercurrences and was discharged with 5-month of life. We had another case of primary hypothyroidism developed in a 2-month old male premature newborn who required prolonged TPN (TSH 21.28 mUI/ml, free T4 0.6 mcg/dL). He also had a normal neonatal screening test. Iodine replacement was attempted via a nasoenteric catheter, unsuccessfully (TSH 197.9 mUI/ml after 10 days). Then, thyroxin reposition was initiated due to critical clinical conditions, with a good response (TSH 9.72 mUI/ml 7 days after). In conclusion, iodine deficiency in newborns receiving prolonged total parenteral nutrition may be a frequent cause of transient neonatal hypothyroidism. Hypothyroidism at the beginning of life is associated with permanent severe neurological damage and must be promptly recognized and treated. When diagnosed, hypothyroidism due to iodine deficiency can be easily corrected with iodine reposition.

THYROID AND PEDIATRIC DISEASE

56055 A NOVEL MUTATION IN THE SODIUM/IODIDE SYMPORTER CARBOXY-TERMINUS UNCOVERS A CRITICAL TRYPTOPHAN-ACID DOMAIN REQUIRED FOR PLASMA MEMBRANE TARGETING

Mariano Martín[1], Victoria Peyret[1], Malvina Signorino[1], Graciela Testa[1], Carlos Modenutti[1], Gabriela Sobrero[1], Liliana Muñoz[1], Marcelo Martí[1], Ana María Masini-Repiso[1], Mirta Miras[1], Juan Pablo Nicola[1]

[1] Universidad Nacional del Córdoba

Introduction: Iodide transport defect (ITD) is an autosomal recessive disorder whose hallmark is the inability of the thyroid follicular cell to actively accumulate iodide. ITD is an uncommon cause of dyshormonogenesis congenital hypothyroidism that results from inactivating mutations in the slc5a5 gene – which encodes the sodium iodide symporter (NIS). The clinical and biochemical presentation of ITD include low to absent thyroid and salivary iodide accumulation and, if untreated, the patients develop a variable degree of hypothyroidism, goiter, and even mental retardation. **Objectives:** To determine if a pediatric patient with a clinical phenotype of ITD harbors an inactivating mutation in the slc5a5 gene, and if so, to ascertain the molecular mechanisms of the effect of the mutation on the biogenesis and activity of NIS. **Methods:** The whole coding region of the slc5a5 was PCR-amplified and subjected to Sanger sequencing, and *in silico* computational and *in vitro* functional studies of a newly identified NIS mutation were performed. **Results and conclusions:** We report a novel homozygous missense and loss-of-function mutation in the slc5a5 gene as a cause of ITD in a pediatric patient with dyshormonogenic congenital hypothyroidism. The patient carries a G>A transition at position +1.682 in exon 14 resulting in a Gly to Glu substitution at residue 561 (G561E) not previously reported in public reference exome databases. We show that G561E markedly reduces iodide uptake when the protein is heterologously expressed in MDCK-II cells, because targeting of G561E NIS to the plasma membrane is severely impaired. Replacing G561 with Gln also resulted in severe intracellular retention, suggesting that a bulky side-chain rather than a negative charge at position 561 interferes with NIS cell surface trafficking. Bioinformatics and biochemical analysis indicates that G561E impair the recognition of an adjacent tryptophan-acid domain by the kinesin light chain 2, thus impairing mutant NIS exit from the endoplasmic reticulum and subsequent plasma membrane targeting. Altogether, our results indicate that a small residue at position 561 is required for NIS maturation and plasma membrane trafficking. Of note, comparison of slc5a5 gene sequence across different species indicates a high conservation of the kinesin light chain 2-recognized tryptophan-acid domain.

56057 NOVEL HOMOZYGOUS NA+/I- SYMPORTER (NIS) GENE VARIANTS OF UNKNOWN CLINICAL SIGNIFICANCE ASSOCIATED WITH DYSHORMONOGENETIC CONGENITAL HYPOTHYROIDISM

Juan Pablo Nicola[1], Malvina Signorino[1], Graciela Testa[1], Gabriela Sobrero[1], Liliana Muñoz[1], Mirta Miras[1], Ana Maria Masini-Repiso[1]

[1] Universidad Nacional del Córdoba

Introduction: Iodide transport defect (ITD) is an autosomal recessive disorder whose hallmark is the inability of the thyroid follicular cell to actively accumulate iodide. ITD is an uncommon cause of dyshormonogenetic congenital hypothyroidism that results from inactivating mutations in the sodium iodide symporter (NIS)-coding gene. Clinical manifestations include low to absent iodide accumulation in the thyroid tissue and, if untreated, the patients develop a variable degree of hypothyroidism, goiter, and even mental retardation. **Objectives:** The objective of this work was to investigate the presence of inactivating mutations in the gene encoding NIS in two unrelated pediatric patients with a clinical phenotype of ITD. **Methods:** The genomic DNA encoding all fifteen NIS-coding gene exons were PCR-amplified and further subjected to Sanger sequencing. Moreover, bioinformatics analysis of the newly identified NIS variants was performed using the software Alamut. **Results and conclusions:** We identify two homozygous variants in the DNA sequence encoding NIS in two unrelated pediatric patients with dyshormonogenetic congenital hypothyroidism. The patients were homozygous for the variants c.1673A>C in exon 11 and c.1973C>T in exon 13, respectively. Significantly, both variants were silent but not observed in the genome of 50 healthy controls, and therefore classified as variants of unknown clinical significance. Bioinformatics analysis revealed that both variants are potentially deleterious for normal NIS mRNA splicing to maintain the open reading frame. The variant c.1673A>C would result in the disruption of a splicing enhancer located in exon 11 and retention of intron 11, originating the putative mutant p.P443fsX86 NIS. Whereas c.1973C>T would result in a novel splicing silencer in exon 13 and retention of intron 13, originating the putative mutant T550fsX3 NIS. Future experiments using functional *in vivo* mini-gene splicing assays are required to fully characterize the impact of the variants on splicing defects. In conclusion, we identified two novel NIS variants of unknown clinical significance associated with dyshormonogenetic congenital hypothyroidism. These variants may lead to potential mis-splicing defects causing structural changes in NIS molecules that impair its normal biogenesis and activity, thus leading to congenital hypothyroidism.

56567 RECENT RECOMMENDATIONS FROM ATA'S GUIDELINES TO DEFINE UPPER REFERENCE RANGE FOR SERUM TSH IN THE FIRST TRIMESTER MATCH REFERENCE RANGES FOR PREGNANT WOMEN IN RIO DE JANEIRO

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Introduction: Serum TSH is the marker of thyroid disorders diagnosis and the definition of specific upper reference range (RR) in pregnancy is essential to minimize over or under diagnosis in specific populations. Recently, ATA's guidelines recommended that, in the absence of specific RR for a determined population, a reduction by 0.5 mUI/L from upper RR of non-pregnant women should be more appropriated than applying, universally, the cut-off of 2.5 mUI/L. **Objectives:** To determine the first trimester RR of serum TSH in a sample from the city of Rio de Janeiro. **Methods:** According to National Academy of Clinical Biochemistry Guidelines, a group of 223 pregnant women, with no personal, or familiar, history of thyroid disease, not using drugs or supplements that might influence thyroid function or hormonal measurements and no goiter were included in this sectional study. Additionally this reference group (RG), that also had a normal median urinary iodine concentration (UIC = 212.5 µg/L), did not have circulating anti-thyroperoxidase antibodies (TPO-Ab). Urinary samples were used to assess UIC by ICP--MS method. Twin pregnancy and trophoblastic disease were exclusion criteria. In a second step, we defined a more selective reference group (SRG, n = 155) by excluding those pregnant with thyroiditis pattern in thyroid ultrasound (heterogenic and/or hypoechoic gland) and with circulating anti-thyroglobulin antibodies (TG-Ab). The SRG also had normal iodine sufficiency by demonstrating a normal median UIC. At final step we excluded any pregnant with UIC < 150 µg/L, which might reflects iodine insufficiency (according to OMS). Serum TSH, TPO-Ab and TG-Ab were measured by chemiluminescent assays, with respective reference ranges (for non-pregnant women) of: 0.4-4.3 mIU/L, ≤ 34 U/mL and ≤ 115 U/mL. **Results:** In the RG the mean, median, 2.5th and 97.5th percentiles of TSH were 1.6, 1.4, 0.1 and 4.4 mIU/L, respectively. The mean age was 27.6 ± 5.7 and the mean body mass index was 25.8 ± 5.6 kg/m^2. In the SRG the 2.5th and 97.5th percentiles were 0.1 and 4.1 respectively. In addition, when excluding any iodine insufficiency from SRG, the 2.5th and 97.5th percentiles were 0.2 and 3.8 respectively. **Conclusions:** In the population studied, the upper limit of TSH was above 2.5 mIU/L. The value of 3.8 mIU/L, found when iodine deficiency and thyroiditis (defined by antibodies and ultrasound characteristics) were excluded, showed to match the recent ATA's guidelines recommendation.

THYROID AND PREGNANCY

56707 MULTIGENERATIONAL EPIGENETIC EFFECTS OF IODINE EXCESS ON THYROID FUNCTION

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Maternal environment during pregnancy/lactation has a critical role in shaping the health outcomes of subsequent generations at adult life. Therefore, when a pregnant mother (parental generation; F0) is exposed to an adverse stimulus, her progeny (F1 generation) may also be affected. Additionally, since the germ cells of F1 generation are developing during gestation, a second generation (F2) may also be affected by the adverse stimulus; an event known as the "grandmother effect". Importantly, epigenetic mechanisms are involved in the programming of gene expression in these crucial development periods. Indeed, our previous data indicated that the exposure of rat dams (F0) to iodine excess (IE) during pregnancy/lactation induces primary hypothyroidism in their offspring (F1) through epigenetic mechanisms. The present study aimed to evaluate whether the maternal F0 exposure to IE also interferes with the hypothalamus-pituitary-thyroid (HPT) axis of the F2 generation. For this purpose, female rats from F1 generation – derived from IE-exposed (0.6 mg NaI/L) or control F0 dams – were mated with control male rats. Thereafter, several molecular parameters of HPT axis were evaluated in male/female rats of the F2 generation at adult life. F0 exposure to IE increased TSH serum levels and did not alter serum T3/T4 levels in F2 generation, suggesting a subclinical hypothyroid condition in these animals. Moreover, IE reduced the expression of genes/proteins involved in thyroid hormones synthesis (Tshr, Nis, Tpo, Tg) and thyroid gene regulation (Pax8, Nkx2.1). As demonstrated in F1 generation, the repression of thyroid gene expression observed in indirectly IE-exposed F2 generation was associated with epigenetic mechanisms. Indeed, we observed increased DNA methyltransferases expression and increased DNA methylation in the thyroid of these animals. In addition, our data indicated hypermethylation and reduced acetylation of histone H3. The latter effect seems to be related to reduced histone acetyltransferase activity/expression and increased histone deacetilase activity/expression. In conclusion, our data indicate that the exposure of F0 generation to IE triggered a multigenerational effect on thyroid function, by impairing the activity of the HPT axis in the F2 generation. Altogether, our data strongly suggest that maternal IE consumption should be carefully monitored, since this treatment disrupts thyroid function in several subsequent generations.

56566 SELECTIVE CASE FINDING *VERSUS* UNIVERSAL SCREENING FOR DETECTION OF HYPOTHYROIDISM IN PREGNANCY: COMPARATIVE EVALUATION IN A GROUP OF PREGNANT WOMEN IN THE CITY OF RIO DE JANEIRO

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Introduction: Universal screening for thyroid dysfunction (TD) during pregnancy remains controversial. **Objectives:** To compare case-finding approach *vs.* universal screening in pregnancy. **Methods:** Pregnant women (n = 281), up to the 12th week of gestation, were evaluated in a multiple center cross-sectional study. Exclusion criteria: < 18 years old, twin pregnancy, levothyroxine or antithyroid drug use. Serum levels of TSH, FT4, anti-thyroperoxidase (TPO-Ab) and anti-thyroglobulin (TG-Ab) antibodies were assessed. Overt hypothyroidism (OH) was diagnosed when TSH > 10.0 mIU/L or FT4 bellow the inferior range (with high TSH). We considered two different TSH cutoff values to define subclinical hypothyroidism (SCH): TSH > 2.5 and TSH > 3.8 mIU/L (by reducing 0.5 from the upper limit of TSH for non-pregnant women). Pregnant women at high risk (PHR) for TD were defined according to 2017 Guidelines of the American Thyroid Association (ATA). The Zulewski's clinical score was applied to assess signs and symptoms of hypothyroidism. **Results:** PHR prevalence was 72.6%, with none patient showing signs/symptoms of OH. Additionally, 31.1% had clinical scores compatible with SCH. Considering PHR, and including SCH symptoms, 77.2% should be screened for TD. Of these, 20.6% had TSH > 2.5 mIU/L, comparing to 25.8% of the women that would not be screened by ATA's guidelines (control group); p = 0.23 [OR = 0.74 (IC: 0.4-1.4)]. Considering > 3.8 mIU/L to define SCH, 4.2% of PHR had SCH *vs.* 8.1% in the control group [p = 0.183; OR = 0.50 (0.2-1.5)]. OH was diagnosed in 0.5% (*vs.* 1.6%; p = 0.40). Regarding the presence of autoimmunity, 5.5% of PHR were TPO-Ab positive (*vs.* 6.3%; p = 0.51), and 8.8% were TPO-Ab and/or TG-Ab positive (*vs.* 9.4%; p = 0.52). Considering PHR, excluding those patients with milder symptoms, 20.4% had TSH > 2.5 mIU/L (*vs.* 25.3%; p = 0.234) and 4.0% had TSH > 3.8 mIU/L [*vs.* 8.0%; p = 0.14 and OR = 0.48 (IC: 0.2-1.4)]. OH was diagnosed in 0.5% (*vs.* 1.3%; p = 0.47), 5.9% were TPO-Ab positive (*vs.* 5.2%; p = 0.54) and 9.3% were TPO-Ab and/or TG-Ab positive (*vs.* 7.8%; p = 0.45). Testing only PHR, 31.7% of patients with TSH > 2.5 mIU/L and 42.9% of those with TSH > 3.8 mIU/L would be missed. Even adding milder symptoms as risk factors, 26.7% of patients with TSH > 2.5 mIU/L and 35.7% with TSH > 3.8 mIU/L would be missed. **Conclusion:** The prevalence of TD in pregnancy is common and testing only the PHR in the targeted high-risk case-finding approach would miss around 1/3 of all hypothyroid patients.

THYROID CANCER BASIC

55811 AMP-KINASE INCREASES GLUCOSE UTILIZATION AND INDUCES APOPTOSIS IN PAPILLARY THYROID CANCER CELL LINE THROUGH INCREASED REACTIVE OXYGEN SPECIES

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Introduction: Tumor survival depends on many changes in metabolic status. These adaptations include changes in the expression and activity of AMP-activated protein kinase (AMPK). Although AMPK has been extensively studied in several models, little is known about its role in tumor progression, especially in thyroid metabolism. **Objective:** To study how AMPK is activated in papillary thyroid carcinomas (PTC), we used a PTC-derived cell line (BCPAP) to analyze cellular metabolic responses to AMPK stimulation with its pharmacological activator, 5-aminoimidazole-4 carboxamide ribonucleoside (AICAR). **Methods:** The MTT assay was used to test cell viability in presence of 2-deoxy-glucose (2DOG); Oligomycin (Olig); AICAR (1 mM) and 1 mM N-acetyl cysteine (NAC) for 24h to evaluate the role of ROS on cell death. Glucose uptake and lactate production was measured by colorimetric methods. Oxygen consumption rate was measured using high-resolution respirometry. ATP content was measured using luciferin-luciferase assay. Hexokinase (HK) enzymatic activity was measured using coupled system to NADPH oxidation. The levels of reactive oxygen species (ROS) were determined using 2'7'-dichlorodihydrofluorescein diacetate (DCFH-DA) and apoptosis was measured by Annexin V. **Results:** BCPAP cells have high glycolytic efficiency, showed 2-fold higher glucose consumption and lactate production rates than the non-tumoral cell line NTHY-ori. This metabolic characteristic was abolished in presence 10 µM compound C, of AMPK inhibitor. The reduction of cell viability in the presence of 2DOG confirms the dependence of BCPAP cells on the glycolysis pathway. BCPAP cells showed higher mitochondria-associated HK activity, but AICAR treatment further increased cytoplasmic HK activity, and ROS production (1.5 fold), leading to decreased cell viability (4 fold). Apoptosis was rescued by NAC, indicating the involvement of ROS-induced cell death together with dependency on mitochondria HK for cell survival. **Conclusion:** Our results suggest that the survival of BCPAP cells involved the HK activity and it is tightly controlled by AMPK.

56599 ABI3, A LINK BETWEEN PI3K/AKT AND WAVE REGULATORY COMPLEX?

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Introduction: We have previously reported that ABI3 expression is lost in most follicular thyroid carcinomas. Restoration of ABI3 expression in a follicular thyroid cancer cell line (WRO), significantly inhibited cell growth, invasiveness, migration and reduced tumor growth *in vivo*. We further demonstrated that ABI3 is epigenetically silenced by promoter methylation in follicular thyroid carcinomas, suggesting that ABI3 is a tumor suppressor gene. However, little is known about the molecular mechanism by which ABI3 exercises these tumor suppressive effects in thyroid cells. **Objectives:** To investigate the molecular mechanism by which ABI3 exerts its tumor suppressive effects in FTC. **Methods:** Cell lysates from WRO cells stably transfected with either ABI3 or control were incubated with Human Phospho-Kinase Array Kit and Human Apoptosis Array Kit. In order to visualize enriched pathways, Kinase Enrichr analysis (KEA) tool was used. The immunoprecipitation combined with mass spectrometry (LC-MS/MS) was used to identify ABI3-interacting proteins. **Results:** We here show, for the first time, that ABI3 is a phosphoprotein that modulated distinct cancer-related pathways in thyroid cancer cells. When we applied KEA analysis, an alternative approach to recognize signaling pathways, we found that PI3K substrates were enriched. The expression of PI3K/AKT pathway components were confirmed in two follicular thyroid carcinoma cells (WRO and FTC133) by western blot. Forced expression of ABI3 in WRO and FTC133 markedly decreased the phosphorylation of AKT (T308 and S473) and the downstream-targeted protein pGSK3β (S9). With immunoprecipitation we identify ABI3-interacting proteins that may be involved in modulating or even integrating signaling pathways. We identified 37 ABI3 partners, including several components of the canonical WAVE regulatory complex (WRC). These findings suggested that ABI3 function might be regulated through this protein complex. Both, pharmacological inhibition of the PI3K/AKT pathway and mutation at residue S342 of ABI3, which is predicted to be phosphorylated by AKT, provided evidences that the non-phosphorylated form of ABI3 is preferentially present in the WRC protein complex. **Conclusion:** Our findings suggest non-phosphorylated form of ABI3 might be associated with its tumor suppressor effects and that ABI3 might link PI3K/AKT with WRC complex.

56618 ANAPLASTIC THYROID CANCER METABOLISM: IMPLICATION OF *IN VITRO* TUMOR AND STROMAL CELLS INTERACTIONS

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Introduction: Thyroid cancer is the most common endocrine malignancy, with rising incidence. Anaplastic thyroid cancer (ATC) is one of the most aggressive tumors. Characterized by its undifferentiated cells, it spreads quickly to distant organs and does not respond well to therapy. It is well known that genetic abnormalities in oncogenes and/or tumor suppressor genes promote tumorigenesis. Emerging evidences, however, have shown that tumor stroma has a crucial influence on cancer development and progression as well. Dysregulated metabolism within the tumor stroma is critical to the process of tumorigenesis, however studies analyzing the role of multicompartment metabolism in ATC are lacking. **Objective:** To investigate whether the interaction of ATC cells-fibroblasts (main component of tumor stroma) reprograms their cellular metabolism. **Methods:** We used an *in vitro* ATC cell (8505c cells)-fibroblast (MRC-5 cells) transwell co-culture system and measured a variety of metabolic parameters by flow cytometry, RT-qPCR, ELISA and Western blot analysis, as depicted in the next section. Statistical analysis was performed using Student's t test. **Results:** We showed that during co-cultures, fibroblasts increased reactive oxygen species (ROS) production, the transcript and secretion of the inflammatory cytokine IL6, the mRNA expression of two glycolytic enzymes, lactate dehydrogenase A (LDHA) and enolase 1 and the mRNA and protein levels of glucose transporter 1 (GLUT1). Conversely, co-cultured ATC cells showed only reduction in GLUT1 and LDHA expression. High ROS levels induce oxidative stress that may trigger the activation of hypoxia-inducible factor 1α (HIF-1α), leading to inflammation and glycolysis. Therefore, we analyzed its mRNA expression in the co-cultures and registered an increase in fibroblasts co-cultured with thyroid cells. In contrast, we did not observe significant changes of this transcription factor in the thyroid cells co-cultured with fibroblasts. **Conclusions and discussion:** Our findings provide *in vitro* evidences of a reprogrammed metabolism by stromal-thyroid tumor cells interactions, suggesting their participation in ATC development and progression. The understanding of these events may have profound clinical repercussions by the implementation of new biomarkers for tumor detection and novel therapeutic strategies to allow the manipulation of the deregulated tumor metabolism and hence reduce or eradicate the tumor.

56056 CARBOXY-TERMINAL SIGNALS REGULATE SODIUM/IODIDE SYMPORTER TARGETING TO THE PLASMA MEMBRANE

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Introduction: The sodium/iodide symporter (NIS), a 643 amino acid glycoprotein expressed at the plasma membrane of thyroid follicular cells, mediates iodide accumulation for thyroid hormone biosynthesis and radioiodide transport for diagnosis and treatment of thyroid cancer. The cloning of NIS provided the basis to investigate the decrease in iodide accumulation in thyroid cancer relative to healthy thyroid cells. Instead of finding only the expected lower NIS expression, the majority of thyroid cancers showed a surprisingly NIS overexpression as compared to the surrounding normal tissue but retained intracellularly. Therefore, it is of considerable clinical relevance to elucidate the mechanisms underlying NIS plasma membrane targeting, a pursuit that could lead to new therapeutic interventions to increase the effectiveness of radioiodide therapy. **Objective:** Short linear motifs have been shown to participate in protein sorting along the secretory pathway. Therefore, we investigated the role of these motifs in NIS transport to the plasma membrane under physiological conditions. **Material and methods:** Short linear motifs on human NIS carboxy terminus were identified using *in silico* computational analysis. We then performed site-directed mutagenesis to disrupt these motifs and functional *in vitro* studies were performed on MDCK-II cells. **Results and conclusions:** The NIS mutant lacking the carboxy-terminus (Δ546-643) is intracellularly retained in MDCK-II cells, thus suggesting that its carboxy-terminus may act as a determinant in anchoring adaptor required for NIS sorting to the plasma membrane. *In silico* analysis revealed different putative short linear motifs frequently involved in plasma membrane proteins targeting to the cell surface. Therefore, we generated deletion mutants of the carboxy-terminus (Δ546-598, Δ578-618, Δ618-634, Δ634-639, Δ640-643) and site-directed mutants of putative sorting motifs (V580A, L583A, L587A, V588A, L594A, L612A, E621A). Functional evaluation revealed that the NIS mutant Δ546-598 containing a putative tryptophan-acidic motif (W565D566) is intracellularly retained. Moreover, we demonstrated that the PDZ binding-motif T640NL643 is not necessary for NIS sorting to the plasma membrane. Although the molecular mechanisms that determine NIS plasma membrane targeting in thyroid cells remain elusive, here, we provide evidence that the carboxy-terminus contains crucial information for NIS functional cell surface expression.

56674 THE OVEREXPRESSION OF LIN28 CHANGES THE EXPRESSION OF MICRORNAS AND THYROID CANCER BEHAVIOR

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Introduction: MicroRNAs(miRNAs) are involved in post-transcriptional gene regulation by repressing the stability and the translation efficiency of their target messenger RNAs. MiRNA expression is altered in cancer, acting as oncogene or tumor suppressor. The miRNA biogenesis involve the participation of RNA-binding proteins (RBP) as an essential regulators of miRNA content in the cell, blocking the miRNA maturation and activating the degradation. The best characterized molecular function of RBP and miRNA is between, let-7 and LIN28, which blocks the let-7 maturation. However, the role of LIN28 in thyroid cancer biology remains to be investigated. **Objectives:** Evaluate the LIN28B function and its relationship with the global miRNA expression change in papillary thyroid cancer. **Methods:** Overexpression of LIN28B was generated in papillary thyroid cancer, TPC cell line transfected with pMSCV/LIN28B-(TPC-LIN28B) and the control line with empty pMSCV--(TPC-Ø). Stable cell lines were obtained by puromycin selection and total RNA and small-RNAs were isolated. The global miRNAs expression was verified in TPC-LIN28B and in TPC-Ø cell by large scale Microarray Analysis using GeneChip® miRNA 3.0 Array (Affymetrix). The differential modulated of miRNAs were based on fold change alteration (>± 2-fold change), and the list of most up and down expressed miRNAs were generated. To identify the influence of LIN28 in blocking miRNA expression, *in silico* analysis looking for the consensus binding site for LIN28 in down-regulated miRNAs were performed using the MiRBase-database (Release 21) and BLAT-Genome Browser®. The cell proliferation and viability assay (MTT) were performed. **Results:** Enhancing the LIN28 in TPC cells, modulate the expressed miRNA in TPC-LIN28. The most up-regulated miRNAs was miR-221 and the miRNA most down-regulated was miR-3185. *In silico* analysis identified that most of down-regulated miRNAs have one or more sequences identified as binding sites for LIN28, suggesting a potential interaction that could influence the miRNA maturation. Furthermore, the overexpression of LIN28B in TPC cell line enhanced the cell proliferation and increased the cell viability. **Conclusion:** Overexpression of LIN28, promote a wide modulation of miRNA and reveals a set of miRNA not yet related with LIN28. The finding of several miRNA potentially targeted by LIN28B, shows a new understanding in controlling the miRNA expression and biological behavior in thyroid cancer.

56689 BRAFV600E MUTATION MAY INDUCES CANCER CELLS "CAMOUFLAGE" IN PAPILLARY THYROID CANCER

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Introduction: Although papillary thyroid carcinoma (PTC) usually has an excellent prognosis, about 5% to 10% of patients have an aggressive disease that accounts for almost all PTC related mortality. The main molecular finding in PTC is the activating mutation BRAF V600E that has been associated with more aggressive features, advanced tumor stages and higher risk of recurrence and disease-specific mortality, and has emerged as an independent poor prognostic marker for PTC. Recent studies demonstrated that malignant cells harboring BRAF mutation secrete a series of chemokines, which are involved in recruitment of tumor-associated macrophages (TAMs), which are strongly associated with thyroid tumor progression. Additionally, expression of CD163, a M2 macrophage marker, in tumors cells has been associated with tumor recurrence and mortality in solid tumors. **Objectives:** To investigate if one of the mechanisms by which BRAF mutation may lead to a more aggressive phenotype is the recruitment of TAMs, and to evaluate the relationship between CD163 expression in cancer cells and its clinical significance in PTC. **Methods:** CD163 expression in tumor cells and TAMs were evaluated in 144 primary PTC (78 metastatic and 66 non-metastatic) by immunohistochemistry. We selected some PTCs that expressed CD163 in tumor cells and some with no expression to evaluate expression of another macrophage marker (CD68) and the thyroid cell marker, thyroglobulin (TG). All primary PTCs were analyzed for BRAFV600E mutational status. To verify the role of BRAF in CD163 expression, we performed co-culture of thyroid cancer cell lines, BCPAP and WRO (with or without BRAF mutation) with a human monocyte cell line (U973). **Results:** 70 out of 144 (49%) PTCs were positive for CD163 in > 10% of tumor cells and it was statistically associated with the presence of BRAFV600E mutation. TAMs CD163+ significantly correlated with lymph node metastasis and vascular invasion. We also found a matched expression of macrophage antigens in tumor tissue (CD68 and CD163). Immunostaining of TG was positive confirming thyroid cell origin. Our *in vitro* analysis confirmed that BRAF induces expression of specific macrophage surface antigens in thyroid tumor cells. **Conclusion:** Our *in vivo* and *in vitro* analysis demonstrated that BRAF induces expression of immune markers by cancer cells suggesting a new mechanism to escape from cell-mediated immunity and may indicate a pro-metastatic state.

56558 HOPX HOMEOBOX GENE EXPRESSION AND METHYLATION STATUS IN DIFFERENTIATED THYROID CANCER

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Introduction: Homeodomain-only protein X (HOPX) gene has been considered a potent tumor-suppressor and its inactivation usually involves HOPX-β transcript promoter methylation in several cancer types, leading to a more aggressive phenotype. The correlation between HOPX-β regulation and differentiated thyroid cancer (DTC) remains unknown. **Objective:** The objective of this study was to investigate the HOPX-β mRNA expression and promoter methylation in DTC. **Methods:** Clinical, pathological data and paraffin thyroid tumor tissues from 21 patients with DTC and 6 with benign tumor s (T) and their non tumoral parenchyma (NT) were collected. Tumor cell lines (FTC238, NPA and WRO) were treated with the demethylating agent 5-aza-dC. HOPX-β mRNA expression was assessed by qRT-PCR, and methylation status by quantitative methylation specific PCR (Q-MSP) and refereed as percent of methylated reference (PMR). **Results:** The HOPX-β mRNA mean normalized expression (MNE) was significantly higher in FTC238 and NPA cells treated with 5-Aza compared to untreated cells. At all, 14/21 (67%) T DTC group had lower HOPX-β mRNA expression compared to NT. HOPX-β mRNA MNE reduction was observed in malignant T group when compared with their NT (4.44 ± 10.92 AU *vs.* 8.85 ± 22.17 AU) ($P < 0.05$). No difference observed in the benign group. Q-MSP analysis of 14 DTC samples who presented downregulation of HOPX-β mRNA showed no significant changes in PMR value when compared with corresponding NT (0,28 ± 0,15 AU *vs.* 0,53 ± 0,15 AU; $P = 0.47$). **Conclusion:** We observed considerable downregulation of HOPX-β mRNA expression in DTC samples and in FTC238 and NPA cell lines, but not followed by high HOPX-β promoter methylation levels, contrasting with what have been shown for other cancers. This raise the possibility that thyroid tissue might use HOPX-β promoter methylation-induced silencing in ways different than pancreas, colon and gastric epithelial tissues. Reduced HOPX expression could result from genetic mutation/deletions or epigenetic histone deacetylation and further analysis would establish the significance of HOPX-β regulation in DTC pathogenesis. **Financial support:** Fapesb (Fundação de Amparo à Pesquisa no Estado da Bahia, Edital 011/2013; TOU RED010/2013) and Fapesp # 2013/195983.

56600 IMPACT OF BRAFV600E MUTATION ANALYSIS ON AMERICAN THYROID ASSOCIATION RISK CLASSIFICATION AND OUTCOMES IN PAPILLARY THYROID CANCER PATIENTS

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Introduction: The B-RAFV600E mutation has been associated with aggressive clinicopathological features in papillary thyroid cancer (PTC). However, its prognostic role is still controversial. Notwithstanding, the American Thyroid Association (ATA) included the B-RAFV600E mutation analysis in the 2015 risk classification system. **Objectives:** To evaluate the impact of the B-RAFV600E mutation on the ATA risk classification and outcomes of patients with PTC. **Methods:** PTC unselected individuals from a cohort attending the thyroid outpatient clinic of a university based hospital who had analysis of the B-RAFV600E mutation were included in this study. Patients were classified as having low, intermediate and high recurrence risk according to the 2009 ATA risk classification system. The mutation was assessed by PCR and sequencing. The impact of mutation analysis was evaluated in the reclassification on the ATA risk system and disease outcomes. Persistent disease was defined as the presence of clinical or radiological and/or biochemical disease (thyroglobulin under suppression > 1 ng/mL and/or stimulated thyroglobulin > 2 ng/mL). **Results:** Of the 133 patients evaluated, 106 (79.7%) were women, and 45 (33.5%) presented the B-RAFV600E mutation. Regarding the extension of disease, median tumor size was 1.7 cm (P25-75 1.0-3.0); 66 (49.6%) patients had lymph node and 9 (6.8%) had distant metastases. According to the 2009 ATA risk system, the risk level was classified as low, intermediate and high in 57 (42.9%), 52 (39.1%) and 24 (18.0%) patients, respectively. The data on B-RAF mutation reclassified 9 (6.8%) patients from low to intermediate risk. After a median follow-up of 6.0 years (P25-75 3.0-9.0), disease status was available for 115 patients: 84 (73%) patients were disease-free and 31 (27%) had persistent disease. Regarding BRAF mutation status, the prevalence of persistent disease was similar in patients with positive and negative mutation: 28.9% *vs.* 26.0% (P = 0.90). In the multivariate analysis, the mutation was also not associated with persistent disease status (RR 1.04; 95% CI 0.62-1.76). Interestingly, none of the patients who had the risk increased from low to intermediate showed persistent disease on follow-up. **Conclusion:** Although B-RAFV600E mutation analysis reclassified a small proportion of patients, it does not add in prediction of outcomes in patients with PTC. The benefit of including the B-RAFV600E mutation analysis in clinical practice must be considered.

56623 MEDULLARY THYROID CANCER PATIENTS UNDERGOING VANDETANIB TREATMENT: CLINICAL DATA FROM THE REAL-WORLD PRACTICE AT A SINGLE TERTIARY CARE CENTRE

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Introduction: Vandetanib (VDT), a tyrosine kinase inhibitor (TKI) that targets ret, VEGFR2 and EGFR, is effective in patients with medullary thyroid cancer (MTC). Despite evidence of improved progression free survival (PFS) and high overall response rate in clinical trials, data on the use of VDT in the real-life clinical setting remain limited. **Objective:** We retrospectively reviewed the efficacy of VDT in locally advanced or metastatic MTC treated at Gustave Roussy. **Methods:** Sixty-five patients were treated with VDT between 2006 and 2015, as first line treatment in 50 patients and as second-line treatment in 11. Four patients were excluded for incomplete data. **Results:** There were 61 patients (74% men). Mean age was 46 years and 7 had hereditary MTC. 66% had metastatic disease in the mediastinum, liver (79%), bones (72%), or lung (59%), and 2 had only locally advanced disease. At the time of evaluation, with a median time of 40 months since VDT treatment initiation and a median treatment duration of 27 months (range 1,1-131 months), 10 patients were still receiving VDT for a median duration of 103 months (range 13-128 months). 36/61 patients discontinued treatment for disease progression after a median treatment duration of 24 months (range 1,8-80 months) and 13 patients for adverse events. PFS at 2 and 5 years were 70% (95% CI 59%-83%) and 38% (95% CI 24-54%), respectively. Best tumor response was a complete response in 3 patients, a partial response in 28 (46%), stable disease in 27 (44%), and progression in 3 patients (5%). Median decreases in tumor size according to RECIST were -18% and -38% for 1st and 2nd line VDT, respectively. **Conclusions:** These findings suggest that the introduction of VDT as molecular-targeted agent resulted in favorable outcomes in MTC patients. **Support:** Capes.

56700 PAPILLARY THYROID CANCER-DRIVING ONCOGENE BRAFV600E PROMOTES ABERRANT TOLL-LIKE RECEPTOR 4 OVEREXPRESSION

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Introduction: Emerging evidence suggests that hyperactivity of Toll like receptors (TLRs) signaling promotes tumor survival signals, thus favoring tumor progression. Recently, aberrant TLR4 overexpression was evidenced in papillary thyroid carcinomas (PTC). **Objective:** To study the mechanisms underlying TLR4 overexpression in PTC harboring the BRAFV600E mutation. **Methods:** TLR4 expression was studied in thyroid tissue derived from human PTCs and transgenic mice expressing BRAFV600E in thyrocytes (Tg-BRAFV600E mice) (IHC, RT/qPCR). BRAFV600E-positive PTC cell line BCPAP and PCCl3 cells expressing BRAFV600E in response to doxycycline (PC/BRAFV600E) were used to study BRAFV600E-driven TLR4 expression (western blot, RT/qPCR, siRNA silencing, luciferase assay). The Cancer Genome Atlas (TCGA) database was used to perform combined analysis. **Results:** We evidenced TLR4 overexpression in PTCs compared to normal thyroid tissues. Moreover, match-samples of primary PTCs and its lymph node metastasis showed a significant upregulation of TLR4 levels in the metastatic tissues. In agreement, TLR4 expression was increased in the thyroid tissue of Tg-BRAFV600E mice compared to littermate controls. Furthermore, we demonstrated functional TLR4 expression in PTC cells models which evidenced an increased NF-κB transcriptional activity in response to the exogenous TLR4-agonist lipopolysaccharide. TCGA data analysis revealed that patients with BRAFV600E-positive tumors and high TLR4 expression have shorter disease-free survival. Consistently with transcriptomic data showing correlation between TLR4 expression and ERK activation score, conditional BRAFV600E expression in PC/BRAFV600E cells upregulates TLR4 protein levels. Moreover, chemical blockage of MAPK/ERK signaling abrogated BRAFV600E-induced TLR4 expression. Deletion analysis of TLR4 promoter revealed a critical MAPK/ERK-sensitive ETS binding-site involved in BRAFV600E responsiveness. Furthermore, we evidenced that the ETS binding factor ETS1 is critical for BRAFV600E-driven MAPK/ERK signaling-mediated TLR4 gene expression in PTCs. **Conclusions:** Increased TLR4 expression in PTCs would be a functional consequence of deregulated MAPK/ERK/ETS1 signaling as a result of thyroid tumors-drivers oncogenes such as BRAFV600E. Considering the oncogenic ability of aberrant NF-κB signaling activation in the promotion of thyroid tumor growth, our results suggest a pro-oncogenic potential of TLR4 downstream signaling in thyroid tumorigenesis.

THYROID HORMONE ACTION

56692 INVOLVEMENT OF THE SPHINGOLIPID INTRACELLULAR SIGNALING PATHWAY IN THE EFFECTS OF TRIIODOTHYRONINE (T3) ON DENDRITIC CELL (DC) ACTIVATION

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Introduction: We reported that mice DCs, the main antigen presenting cells, express thyroid hormone receptor β1 with a preferential cytoplasmic localization and that physiological levels of T3 promote their maturation and their ability to direct adaptive responses towards a Th1-type profile. Mechanistically, T3 effects involved activation of Akt independently of PI3K. Besides, sphingolipids revealed as key elements in signal transduction cascades, regulate events related to death and survival of cells. The major bioactive sphingolipids include: sphingosine, sphingosine-1-phosphate (S1P), ceramide and ceramide-1-phosphate. Noteworthy, there is evidence that they are involved in the non-classical Akt activation. **Objectives:** We aim to further disclose the molecular mechanism underlying the effects of T3 on DC functioning, in particular in the non-classical Akt activation. For this purpose, we characterized the intracellular pathway mediated by sphingolipids in DCs and initiated the studies of its involvement in T3-mediated DC activation. **Methods:** Mice immature DCs were cultured for 18h with T3 (5 nM) in the presence of chemical inhibitors of the sphingolipids pathway (GW4869: neutral sphingomyelinase, nSMAse and SKI: sphingosine kinases, SphK). DC viability was analyzed by Annexin V/7-AAD assay (flow cytometry). Intracellular and secreted IL-12 production was assayed by flow cytometry and ELISA, respectively (IL-12 is a sensitive marker of T3 action on DCs). The mRNAs expression coding the enzymes nSMAse, acid SMAse, SphK and ceramide kinase was evaluated through RT-PCR. Statistics: ANOVA/SNK test. **Results:** In this study we demonstrated that DCs express mRNA for the enzymes evaluated which are essential for the balance between intracellular levels of interconvertible sphingolipids. Furthermore, exposure of maturing DCs to both inhibitors significantly suppressed their ability to produce IL-12 in response to T3. To note, neither GW4869 nor SKI induced any significant effect on DC viability. **Conclusion:** Our results suggest that S1P is involved in T3 effect on DC maturation in agreement with our previous report indicating an increase of Akt activation in T3-stimulated DC. These findings provide evidence for active involvement of the sphingolipid signaling pathway in the effects registered by T3 treatment to DCs. Considering the therapeutic impact we reported for T3-treated DCs, these results provide molecular tools to manipulate the immunogenic potential of DCs.

56693 THE TYPE 3 DEIODINASE IS HIGHLY EXPRESSED IN BREAST CANCER

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Introduction: Thyroid hormone (TH) status regulates the balance between proliferation and differentiation in normal and tumoral cells. An altered TH status can contribute to the development of tumors. Intracellular T3 bioavailability is controlled in a tissue-specific manner, depending primarily on its activation by type 2 deiodinase (D2) and inactivation by type 3 deiodinase (D3). D3, a known fetal protein, is mainly responsible for TH inactivation. D3 is reactivated in several human neoplasias, and it has been associated with tumor behavior. Breast cancer is the most common cancer in women worldwide. D3 status in breast cancer is unknown and could contribute to tumor progression. **Objectives:** To evaluate D3 expression in breast cancer and its correlation with tumor subtype and TNM staging. **Methods:** D3 expression in breast cancer samples was analyzed by immunohistochemistry (IHQ) using anti-D3 antibodies. Samples were classified into four subtypes: luminal A, luminal B, triple negative and HER2. D3 expression was quantified by H-score. For further studies, estrogen receptor positive (ER+) (MCF-7) and ER- (MDA-MB-231) cell lines were used. Cell proliferation was analyzed by cumulative population doubling. Cell cycle distribution and apoptosis were assessed by flow cytometry after staining MCF-7 and MDA-MB-231 cells with propidium iodide (PI) and Annexin V/PI, respectively. Protein levels of D3 after treatment with T3 and with/without specific siRNA was evaluated by Western Blotting using anti-D3 antibody and was quantified using image densitometry. **Results:** D3 expression was observed in all breast cancer subtypes analyzed, as well as in ER+ (MCF-7) and ER- (MDA-MB-231) cell lines. Interestingly, MDA-MB-231 cell proliferation was reduced by 35% ($p = 0.004$) after 48 hours of transient D3 silencing (D3 siRNA) whereas MCF-7 proliferation was not significantly affected by D3 transient inhibition in the presence or absence of T3 (100 nM). To further explore the effects of D3 knockout in breast cancer cells, we intend to use CRISPR/Cas9 technology to selectively modulate enzyme expression and intracellular T3 levels in different breast cancer cell lines. **Conclusion:** Our results demonstrate that D3 is highly expressed in breast cancer, and the inhibition of D3 activity is associated with reduced proliferation in an estrogen negative cell line.

56701 TRIIODOTHYRONINE (T3)-STIMULATED DENDRITIC CELLS (DCS) PROMOTE A PRO-INFLAMMATORY ADAPTIVE IMMUNE RESPONSE – *IN VIVO* EVIDENCES

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Introduction: The immune and endocrine systems are in constant communication to maintain homeostasis and orchestrate coordinated responses to imbalances and pathologies. In this sense, we previously reported that mice DCs, the main antigen-presenting cells, express thyroid hormone receptor β1 and that physiological levels of T3 stimulate the maturation of DCs and their ability to direct adaptive responses towards a Th1-type profile *in vitro*, as well as cytotoxic and antitumoral effects in an *in vivo* model of B16 melanoma. Furthermore, *in vitro*, T3 stimulated DC production of the Th17-skewing cytokines and reduced the expression of programmed death-ligand 1 and 2 (PD-L1 and PD-L2). In addition, T3-matured DCs increased the production of IL-17 and decreased the frequency of regulatory T (Treg) cells in allogenic splenocytes. **Objectives:** The aim of this study was to analyze the adaptive immune response induced by T3-stimulated DCs *in vivo* regarding *in vitro* findings and previous therapeutic implications registered by T3-conditioned DC vaccination. **Methods:** Mice bone marrow derived DCs treated with ovalbumin (OVA) and 5 nM T3 (OVA+T3-DCs) for 18 h, were injected i.v. into OTII transgenic mice, which own a four-fold increase in CD4/CD8 peripheral T cell ratio that primarily recognize OVA peptide (OVA323) when presented by the MHC class II molecule. One week later, splenocytes were restimulated *ex vivo* with OVA323, and proliferation, IL-17 and IFN-γ releases, and CD4+CD25+FoxP3+ (Tregs) and programmed death-1 protein (PD-1)+ cells were determined 4 days later by MTT assay, ELISA and FACS, respectively. Statistics: ANOVA/SNK test. **Results:** In OVA+T3-DCs treated mice we demonstrated an increase in splenocytes proliferation and that spleen cells secrete higher IL-17 and IFN-γ levels *vs.* OVA-DCs injected mice. In contrast, splenocytes from OVA+T3-DCs group decreased Treg population and exhibited a reduction of the expression of the inhibitory molecule PD-1, compared to those from OVA+DCs-treated mice. **Conclusions and discussion:** These results reinforce the critical role of T3 in the regulation and maintenance of immune homeostasis since T3-exposed DCs favor the promotion of adaptive immunity towards a pro-inflammatory profile *in vivo*. Our findings have therapeutic implications for the manipulation of the immunogenic potential of DCs to positively regulate the development of protective immunity or negatively control the generation of autoimmune diseases.

THYROID NODULE

56581 A NEW MOLECULAR DIAGNOSTIC TEST BASED ON MIRNA-PROFILING FOR CLASSIFICATION OF THYROID NODULES WITH HIGH SENSITIVITY AND SPECIFICITY

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Introduction: Thyroid nodules are the main clinical manifestation of thyroid's diseases. By ultrasound, it can be identified in up to 76% of the population. Currently, fine-needle aspiration (FNA) pathology review represents the gold standard initial test for diagnosing malignancy. However, FNA cannot classify 15%-30% of nodules, known as indeterminate, which are often referred for thyroidectomy surgery due to the risk of malignancy. The histological post-surgical analysis reclassifies around 70%-80% of cases as benign, highlighting the considerable rate of unnecessary surgeries. Although clinically useful, current available molecular classifiers cannot offer, together, high sensitivity and specificity, limiting its use and application. **Objectives:** We sought to develop a miRNA-profiling-based molecular diagnostic test able to classify indeterminate thyroid nodules into benign or malignant, with high sensitivity and specificity. **Methods:** The expression of 96 miRNA candidates from 40 benign/40 malignant thyroid indeterminate (Bethesda III, IV or V) samples at the FNA pathology review were analyzed by qPCR. The cytology slides and histology post-surgical tissues were double-blinded revised by independent pathologists. Expression data was used for biomarkers selection and signatures generation for the molecular classifier development. **Results:** Based on a signature obtained by the expression of only 18 miRNAs, our molecular classifier achieved 93% sensibility and 86% specificity during validation studies with data from revised indeterminate thyroid nodules. The observed area under the curve (AUC - also known as ROC curve) was 0.944. We also developed a new protocol for miRNA extraction directly from FNA cytology slides. **Conclusion:** We successfully developed a new miRNA-profiling-based molecular classifier, which shows not only a higher sensitive and specificity compared to other commercially available tests, but also a high balanced accuracy. The possibility to use FNA cytology slides as a sample source for testing will avoid the need of new invasive and painful FNA procedures for patients.

56637 PERFORMANCE OF THE ULTRASOUND (US) RISK STRATIFICATION FOR MALIGNANCY OF THE 2015 AMERICAN THYROID ASSOCIATION (ATA) GUIDELINES IN ELDERLY PATIENTS WITH THYROID NODULES

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Introduction: A recent US classification of thyroid nodules has been released by the ATA in order to target thyroid cancer. **Objective:** To validate 2015 ATA Guidelines classification of thyroid nodules based upon US in an elderly population. **Method:** Out of 2,084 patients (70.4 ± 7.6 ys) (92% female sex) that underwent fine needle aspiration biopsy (FNAB) at our Institution from 2008-2016, 1340 with complete data were included for the validation (ATA1: benign, ATA2: very low, ATA3: low, ATA4: intermediate and ATA5: high risk of malignancy). Histopathological results were recorded but only the Bethesda (B) system for reporting thyroid cytopathology was considered the gold standard. Malignant (M) cytology included BV/VI categories and indeterminate/malignant (I/M) cytology comprised BIII/IV/V/VI. ATA categories were then dichotomized as high risk *vs.* all the rest. Thyrotropin (TSH) values were studied across ATA categories. Chi2 test was used to compare malignancy rate among ATA categories with Bonferroni's correction for multiple comparison. **Results:** Histological findings were obtained in 84 patients, 32% were malignant. Cyto-histological concordance was significant (Kappa 0.72, $p < 0.001$). M cytology was found in 2% of the 1340 nodules and I/M in 8%. Out of all US findings, microcalcifications, hypoechoic pattern and irregular margins were individually associated to M cytology ($p < 0.01$). An almost significant association was found between the ATA category system and M cytology ($p = 0.08$) which achieved statistical significance when I/M cytology was used instead ($p < 0.001$). When ATA categories were dichotomized, high risk category was significantly associated with M cytology (OR 2.3 CI 1.0-5.0 $p = 0.03$). TSH was higher in patients with M cytology than in the rest (+36%, $p < 0.05$). ROC curve analysis showed that TSH = 4 mU/L was associated with M cytology with a sensitivity of 0.70 and specificity of 0.88. As risk increased across ATA categories the proportion of patients with TSH > 4 mU/L also increased. Finally, TSH > 4 mU/L + ATA5 classification emerged as significant predictor of M cytology (OR 4.5 CI 1.01-20.5, $p < 0.05$). **Conclusion:** The use of the high risk US category according to the 2015 ATA Guideline enabled the detection of M cytology and may be useful in elderly patients in whom nodular disease is both more frequent and aggressive. Higher TSH values were related to higher risk categories and might be considered together with US findings to select a nodule for FNAB.

56654 THE ROLE OF INSULIN RESISTANCE AND THE EFFECT OF METFORMIN USE ON VOLUME OF BENIGN THYROID NODULES

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Introduction: It has been shown that insulin might be involved in the pathogenesis of thyroid growth. Previous studies suggest that metformin (MTF) therapy decreased thyroid volume and nodule size in subjects with insulin resistance (IR). **Objectives:** To evaluate the impact of IR and metformin use on the volume of benign thyroid nodules (TNs). **Methods:** Twenty-seven individuals with benign TNs (forty-six TNs) were included in a randomized clinical trial to placebo (P) or MTF use. Previous fine needle aspiration confirming the diagnosis was necessary to inclusion. Exclusion criteria were: nodules with a predominantly cystic pattern, pregnancy, diabetes, acromegaly, previous use of MTF, levothyroxine, corticoid or any weight loss medication in the past six months, hepatic or cardiac insufficiency, creatinine levels > 1.4 mg/dL and MTF intolerance doses > 1.0 gram/day. Similar tablets of MTF and placebo were given and patients were instructed to take 3 tablets/day of MTF (500 mg/tablet). Thyroid volume, as TN volume, was assessed by ultrasound, both in the beginning and six months after randomization, by the same researcher blinded regarding location group. Blood samples to measure: TSH, FT4, TPO-Ab, lipid profile, glucose and insulin were done after 8h fasting. **Results:** Preliminary results with 15 subjects (30 TNs: P = 16; MTF = 14) completing 6 months trial showed that both groups were similar regarding baseline characteristics (age, BMI, sex, TSH levels, HOMA-IR, thyroid gland volume and TN volume). HOMA-IR variations throughout the time correlated with thyroid volume ($rs = 0.49$; $p = 0.004$) and BMI variations ($rs = 0.433$; $p < 0.01$) and tended to correlate with TNs volume variations ($rs = 0.23$; $p = 0.10$). Taking into account the nodules that have grown, 14,3% remained with IR (*vs.* none in the group without this endpoint; p = NS). Serum TSH reduced significantly with MTF use (-0.15 *vs.* +0.22 mIU/L; $p < 0.01$), as did BMI (-0.6 *vs.* + 0.1 kg/m^2 with placebo; $p = 0.025$). An increase in nodule volume (+11.4%) was observed in placebo group (*vs.* +3.1% in MTF; $p = 0.55$). **Conclusion:** These preliminary results provide support for an association between IR and thyroid growth. MTF reduced serum TSH and despite did not impact significantly TNs volume changes more follow-up time is necessary to evaluate if the non-significant increment observed in P group will differ statistically from MTF group changes.

THYROID REGULATION

56583 AUTOCRINE ACTIONS OF THYROID HORMONE (T3) REGULATE EXPRESSION OF GENES INVOLVED ON POST-TRANSCRIPTIONAL AND POST-TRANSLACIONAL EVENTS IN THYROID FOLLICULAR CELLS

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Thyroid hormone plays an important role in developmental, growth and metabolic processes. It acts through specific nuclear receptors bound to thyroid response elements on target genes activating/repressing their transcription or through receptors on the plasma membrane triggering intracellular signaling pathways, by non-genomic mechanism. Thyroid dysfunctions are the second major cause of metabolic disorders around the world. So, many studies have been carried out intending to clarify all aspects of thyroid hormone actions on different tissues. However, little is known about the role of TH on the gland in which it is produced. In this sense, the aim of this study was to evaluate, through New Generation Sequencing methodology (RNAseq) the gene expression profile of thyroid follicular cells in the presence or absence of TH. Pccl3 cells were maintained in TH-free medium (HYPO) for 24h. Cells were divided into two groups: one remained in the HYPO medium and the other was treated with 3,3',5 triiodothyronine (T3) at concentration of 10-7M for 24h. Afterwards, cells were lysed for total RNA extraction and submitted to ribosomal RNA depletion assay (Ribominus™). cDNA libraries were prepared using rRNA-free samples and then sequenced by SOLiD® commercial sequencing platform. The raw data obtained in the sequencing were statistically analyzed to build the list of genes differentially expressed, of which 85% were upregulated, while 15% were down-regulated by T3. Among genes that were upregulated two were selected for validation: gene Pfdn1 (LogFoldChange = 1.68, p = 9.2E-05) which is involved in protein folding and gene Fam103a1 (LogFoldChange = 1.94, p = 1.26E-05) which is responsible for adding CAP (7Rmethylguanosine) into mRNA during transcription. After validation of the sequencing data by RT-qPCR, we also evaluated the expression of both genes under T3 treatment at 10-9 M for 1h. In 10-7M of T3 the Pfdn1 mRNA expression increased 2 and 8-fold (*vs.* HIPO) after 1 and 24h, respectively. In the 10-9 M dose, it was observed an increase only after 24h. The Fam103a1 mRNA expression increased approximately 6-fold (*vs.* HYPO) only at the 10-7 M; no effect was observed at the 10-9 M. Data suggest that T3 plays an important role on the mRNAs mcappingc, which is essential for their stabilization and translation rate, as well on the protein folding, which point out to important actions played by TH on post-transcriptional and pos-translational control of gene expression.

56085 REGULATION OF THE NUCLEAR FACTOR NF-κB SIGNALING PATHWAY IN RESPONSE TO THYROID-STIMULATING HORMONE RECEPTOR ACTIVATION

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Introduction: Although activation of NF-κB signaling in thyroid follicular cells downstream to TSH receptor engagement has been reported, the downstream signaling that result in NF-κB activation remain unexplored. Previously, we demonstrated the participation of NF-κB in the upregulation of different genes involved in thyroid hormonogenesis in response to bacterial lipopolysaccharide. Recent data demonstrated that genetic deletion of NEMO in the thyroid tissue lead to apoptotic death of thyroid follicular cells. **Objective:** We sought to elucidate the mechanism that mediates NF-κB signaling activation in response to the activation of the TSH receptor. **Results and Discussion:** TSH treatment leads to PKC-mediated phosphorylation of the IKK regulatory complex, degradation of the cytosolic IκB-α inhibitor, and nuclear translocation of the NF-κB p65 subunit, thus indicating activation of the canonical NF-κB signaling. Moreover, TSH stimulation phosphorylates the kinase TAK-1 and its knock-down abolished TSH-induced IKK complex phosphorylation and the transcriptional activity of NF-κB. Although PKA inhibition did not modulate TSH-induced nuclear recruitment of p65, TSH induces the transcriptional activity of the NF-κB subunit p65 in a PKA-dependent phosphorylation on Ser-276. Additionally, p65 phosphorylation on Ser-276 induced acetyl transferases CBP/p300 recruitment leading to its acetylation on Lys-310, thus enhancing its transcriptional activity. Evaluation of the role played by NF-κB in thyroid physiology demonstrated that the NF-κB inhibitor BAY 11-7082 reduced TSH-induced expression of the proteins involved in thyroid hormonogenesis Of note, the role of NF-κB in thyroid physiology was confirmed assessing TSH-induced gene expression in primary cultures of NEMO-deficient thyrocytes. Moreover, chromatin immunoprecipitation and knock-down experiments revealed that p65 is a transcriptional effector of TSH actions inducing the expression of genes involved in thyroid hormonogenesis. Altogether our results point to NF-κB as a pivotal mediator in the TSH-induced thyroid follicular cell differentiation. Increasing evidence indicates that NF-κB participates in the pathogenesis of autoimmune diseases, being a key factor in the interface between inflammation and cancer. We speculate that a misbalance in TSH signaling regulation could have potential implication in thyroid pathophysiology through the modulation of NF-κB signaling.

THYROID AUTOIMMUNITY

56596 FACTORS ASSOCIATED WITH THE PRESENCE OF CLINICALLY APPARENT OPHTHALMOPATHY IN GRAVES' DISEASE

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Graves' ophthalmopathy (GO) is the major extra-thyroidal manifestation of Graves' disease (GD); however it is clinically apparent in about 50% of the cases. Mechanisms involved in its pathogenesis are partially understood and genetic and environmental risk factors are described. **Objectives:** To evaluate factors associated with the presence or absence of GO in a population of patients with GD. **Methods:** 124 patients with GD were included, 93 (75%) were women. Median age at diagnosis was 42 years (range 19-73). All patients underwent laboratory studies (TSH, T4, T3, TRAb, ATPO, 25OH vitamin D and IGF-1) and ophthalmologic evaluation. Demographic characteristics and biochemical determinations were compared in relation to the presence or absence of orbital disease. **Results:** 94 patients (75.8%) had clinically apparent GO; 64.2% were hyperthyroid, 35% euthyroid and 0.8% hypothyroid. Smoking was present in 40.4% of this population. Comparing patients with or without (n = 30, 24.2%) GO, smokers were at increased risk of eye disease with an odds ratio (OR) of 5.64 (95% CI 1.55-20.47). A cut-off value of TRAb of 34% was identified as a factor of high risk for GO, with a sensitivity of 63.8% and a specificity of 60%. Patients with TRAb ≥ 34% had an OR of 2.65 (95% CI 1.139-6.15) for orbital disease. No other differences were found between both groups. **Conclusions:** Smoking and higher levels of TRAb were identified as risk factors for the presence of clinically apparent GO in patients with GD. Smokers were 5 times more likely to have ophthalmopathy. Higher levels of TRAb were associated with greater risk for GO. When considering patients with TRAb ≥ 34%, the risk of GO was approximately 2.5 times greater. It is important to emphasize the high percentage of GO in this population of patients with GD.

GENETIC

56252 ROLE OF RET POLYMORPHISMS IN MEN2A-ASSOCIATED HYPERPARATHYROIDISM

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Introduction: Multiple Endocrine Neoplasia Type 2A (MEN2A) is an autosomal dominant inherited disease characterized by medullary thyroid carcinoma (MTC), pheochromocytoma and hyperparathyroidism (HPT), with high penetrance and variability of expression. HPT is the less common component of the syndrome (10% to 30% of patients). Several authors have suggested that RET polymorphisms could be associated with susceptibility and prognosis of MTC. **Objective:** To evaluate the frequencies of RET polymorphisms (G691S, L769L, S836S e S904S) in MEN2A-patients and verify the association of RET variants with susceptibility and age-dependent penetrance of HPT. **Methods:** The RET variants G691S, L769L, S836S, and S904S were evaluated in a cohort of 157 MEN2A patients (M = 70, F = 87) attending tertiary teaching hospital. A comparison of RET variants frequencies between patients with and without HPT was performed. Kaplan-Meier curves and Cox regression analysis were used to estimate the effect of RET polymorphisms on the age-dependent penetrance. **Results:** A total of 28 (16.6%) patients presented MEN2A-associated hyperparathyroidism. The mean age at diagnosis was 35.27 years, 55.4% of patients were women. Female subjects had higher risk of HPT development (OR = 2.61; 95% CI = 1.04-6.55). Ninety percent of the patients had RET mutation at codon 634 and 60% had some RET polymorphisms. RET mutations frequencies were similar between patients with or without HPT (P = 0.632). The frequencies of RET variants were as follows: 33.7% G691S, 33.1% L769L, 12.7% S836S and 33.7% S904S and no association was found between the frequencies of these RET polymorphisms and HPT development. However, Kaplan-Meier estimates of cumulative HPT diagnosis yielded distinct curves for patients harboring no or one polymorphism and two or more polymorphisms (P = 0.017). Patients harbored two RET variants exhibited an increase risk for earlier HPT development regardless gender (P = 0.015; OR 3.03; 95% CI 1.24-7.39). **Conclusions:** RET polymorphism alleles have an additive effect on the estimated risk of age-related HPT development in MEN2A patients.

HYPERTHYROIDISM

56652 A RARE FORM OF HYPERTHYROIDISM: MARINE-LENHART SYNDROME

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The coexistence of autonomous functioning thyroid nodules and Graves' disease has been termed Marine-Lenhart syndrome. The syndrome is rare, and prevalence was reported between 2.7% to 4.1%. A 43-year-old woman asymptomatic was referred to our Thyroid Clinic in 2013 for thyroid nodule. She had normal thyroid function: TSH 3.2 (0.4-4.5) uUI/mL, free T4 1.36 (0.93-1.7) ng/dL, TgAb 22.62 (< 115) UI/mL and TPOAb 17.55 (< 34) UI/mL. The thyroid ultrasonography (US) showed simple cyst in the right thyroid lobe, measuring 3.4 x 1.7 cm, with vegetation inside measuring 1.2 x 1.1 cm. The result of US-guided fine-needle aspiration was Bethesda II. Two years later, her TSH was 0.02 (0.4-4.5) uUI/mL and free T4 was in the upper limit of normal 1.68 (0.93-1.7) ng/dL. One month later, the patient complained of palpitations and lost 2 kg. On physical examination, a nodule with 1,5 cm in diameter in the right thyroid lobe was palpated. She had no evidence of Graves' ophthalmopathy or dermopathy. The next TSH was < 0.005 uUI/mL, free T4 was elevated 2.17 ng/dL and TRAb was 6.89 (< 1.75) UI/L. The thyroid US examination (November 2015) showed thyroid gland with normal dimensions, with two heterogeneous solid-cystic nodules in the right lobe, with the dimensions: 1.7 x 1.1 cm and 0.9 x 0.7 cm. The ^{99m}Tc-pertechnetate scintigraphy revealed an avid tracer uptake in the right lobe, corresponding to the nodular lesion demonstrated by thyroid US (February 2016) and thyroid uptake was 2.5% (0.4-1.6). The initial treatment was with metimazol for two month. Subsequently, the patient had radioiodine therapy with iodine-131 (30 mCi) in May 2016. Patient developed hypothyroidism using levothyroxine. Based on these findings, a diagnosis of Marine-Lenhart syndrome, which is Graves' disease associated with autonomous functioning nodules was performed. Radioiodine is successful choice of treatment, because antithyroid drugs regimen will not lead into remission. Besides, the radioiodine dose must be higher when compared of the Graves' disease treatment alone. As a conclusion, physicians should be aware of a possibility of the Marine-Lenhart syndrome in Graves' disease associated with nodular thyroid disease.

56729 ASSOCIATION OF GRAVES' DISEASE AND PAPILLARY THYROID CARCINOMA WITH HIGH RISK OF MALIGNANCY: CASE REPORT

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Simultaneous occurrence of hyperthyroidism and thyroid carcinoma is a controversial issue both in incidence and clinical progression. The objective of this study was to report the case of a patient with Graves' disease (DG) associated with papillary carcinoma of the high risk thyroid. **Case report:** M.C.S.L., 36 years old, male, with clinical and laboratory diagnosis of DG (TSH < 0,01 mcIU/mL (RV: 0,3-4,3), free T4: 5,2 ng/dL (RV: 0,7-1,9), TRAb: 20,6 IU/L (RV: up to 1,75) and thyroid ultrasonography compatible with diffuse goiter with no reported lymph node involvement) associated with ophthalmopathy. Patient with previous biliary lithiasis and with use of antithyroid drugs, evolved with cholestasis and progressive worsening of the symptoms of hyperthyroidism and concomitant ophthalmologic decompensation, even in the course of adjuvant corticosteroid therapy, to improve the ophthalmopathy. Thus, decided surgical follow-up with total thyroidectomy to treatment. Histopathological compatible with toxic nodular goiter associated with classic papillary microcarcinoma (0,9 x 0,6 cm) with infiltration of capsules without reaching adjacent extra-thyroid tissue and metastasis to two adherent lymph nodes, one with extracapsular extravasation. **Discussion:** Incidental thyroid carcinomas in patients with DG are not uncommon, but most of them are presented with low risk histopathological criteria. Pathogenesis of carcinoma development is still under investigation, but several theories are already conveyed, such as the assumption that TSH receptor stimulating antibody (TRAb) may promoting thyroid carcinogenesis as well as the accumulated risk of recurrence and progression of distant metastases in patients with this coexistence, inducing an increase in the aggressiveness of the carcinoma, another theory is about the histological alterations of hyperthyroidism could represent a trigger in the development of thyroid cancer and the other factor implicated in this involvement is the exposure to external radiation of the head and neck, especially in childhood. **Final comments**: Noted, therefore, that the relationship between DG and thyroid carcinoma is not well established, especially in cases of increased aggression of this type of cancer, emphasizing the importance of this report and the need for studies to better understand the development and biological and clinical follow-up of these carcinomas for the purpose of screening and effective approaches to the patients affected.

56685 CAN A SURGICAL PROCEDURE CORRECT HEART FAILURE RELATED TO HYPERTHYROIDISM WITH ATRIAL FIBRILLATION? IF ATRIAL THETHERING IS PRESENT, THE ANSWER IS YES

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AMP, 37 year old female initially diagnosed with Graves' disease in 2010 (TRAb > 40 ui/L –reference > 1,75). She had symptoms for about 24 months before the diagnosis and referred worsening in the previous 6 months with heart failure symptoms. At initial exam, she was clearly thyrotoxic with enlarged thyroid gland (40 g) and atrial fibrillation (AF). She was referred to radioiodine (22 mCi) that resolved her hyperthyroidism in this same year. In spite of thyrotoxicosis resolution, she stayed with persistent AF. Initial echocardiogram showed enlargement of both atriums, an elevated pulmonary systolic arterial pressure (PSAP) with a completely normal ventricular function. She became asymptomatic and started a medical follow up with levothyroxine, carvedilol, spironolactone and aspirin. She returned to work and unfortunately lost medical after 3 years. She presented at our institution in 2016 with decompensated congestive heart failure. She as on her regular levothyroxine dose, carvedilol and spironolactone. The new echocardiogram showed a normal left ventricular ejection fraction (LVEF), enlargement of all four cavities, a mild tricuspid regurgitation and a severe mitral regurgitation suggestive of atrial tethering. A mitral valve replacement with mechanical prosthesis and tricuspid repair was performed. Postoperative transthoracic echocardiogram revealed a mitral mechanical valve, normal LVEF, a normal mitral gradient, mild tricuspid regurgitation and no pulmonary hypertension. At follow-up four months later, she has no symptoms of heart failure. **Discussion:** Atrial fibrillation (AF) can be related to hyperthyroidism and younger patients without comorbidities usually restore their sinus rhythm after resolution of thyroid dysfunction. Persistence of AF is a routine problem in clinical practice but AF persistence inducing mitral insufficiency is a diagnosis recently described as atrial tethering. Functional mitral valve (MV) regurgitation is a known mechanism related to left ventricular dysfunction and enlargement with induction of an imbalance for MV coaptation. Left atrium remodeling (without ventricular dysfunction) inducing abnormal coaptation of MV supposedly implies better prognosis since mitral valve substitution seems to restore normal coaptation and consequently normal left heart function. **Final comments:** We described the first patient with atrial thethering due to AF related to hyperthyroidism completely corrected with MV replacement.

56129 CAN MILD TO MODERATE FORMS OF GRAVES' ORBITOPATHY BE CONSIDERED A CHRONIC DISEASE?

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Introduction: Graves' orbitopathy (GO) is the most important extrathyroid manifestation of Graves' disease (GD), leading to important biological and emotional consequences that interfere with patients' quality of life (QoL). The aim of the study was to validate the Portuguese version of the GO (QoL-GO) questionnaire comparing it with the clinical activity score (CAS), severity of GO (NOSPECS) and the European Group of Graves' Orbitopathy (EUGOGO) classification. **Methods:** A cross-sectional study was carried out including 323 GD patients. The QoL-GO questionnaire was performed in two groups of GO patients. Group 1 included GO patients with absent or minimal eye involvement (CAS < 1, NOSPECS < 1 and EUGOGO absent or minimal). Group 2 included GO patients with a CAS score between 2 and 5; NOSPECS between 2 and 4; and EUGOGO compatible with moderate forms. **Results:** There were 280 females and 53 males, mean duration time since GO diagnosis was 7.12 ± 6.66 years in the studied group with mean age 48.97 ± 14.77 years old. The QoL-GO scores in visual function and appearance domains was associated with CAS, NOSPECS and EUGOGO classifications ($p < 0.001$ in all analyzes). Group 2 patients had worse scores of visual function and appearance in the CAS, NOSPECS and EUGOGO classifications compared to GO patients of group 1 ($p < 0.0001$ in all analyzes). The multivariate analysis identified the EUGOGO classification as a variable associated with the worst performance concerning visual function score ($p < 0.0001$). Additionally, the variables associated with the lowest scores regarding appearance were: age ($p < 0.01$), EUGOGO classification, proptosis and asymmetry between eyes ($p < 0.0001$). **Conclusion:** The QoL-GO was validated for Portuguese, and associated with the CAS, NOSPECS and EUGOGO classifications. Patients with moderate forms of GO presented a significant decrease in QoL. The use of QoL-GO was able to identify patients who need more clinical and psychological support.

56099 CHANGES IN GRAVES' DISEASE PRESENTATION DURING THE LAST 30 YEARS

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Introduction: Graves' disease (GD) is the leading cause of hyperthyroidism; clinically it manifests itself as goiter, orbitopathy and thyrotoxicosis (Merseburg Triad). However, there is little data regarding alterations in clinical presentation in the last 30 years. **Objective:** Evaluate changes in the clinical presentation of GD over the 30 years. **Methods:** The study analyzed 311 patients with GD from 1986 to 2016. These patients were divided in two groups, using the year of diagnosis of GD. Group 1: patients from 1987 to 2006, and group 2: patients from 2007 to 2016. **Results:** In the Group 1 (n = 120) mean ± SD age at diagnosis was 42 ± 0.5 years, 72% were female, TSH and free T4 at the diagnosis were 0.051 ± 0.003 UI/L and 4.33 ± 0.056 ng/dl, respectively. In the group 2 (n = 191) mean age at diagnosis was 42 ± 16 years and 76% of female; mean TSH and free T4 at diagnosis were 0.126 ± 0.011 UI/L and 3.84 ± 2.79 ng/dl, respectively. No significant difference was observed between the groups, regarding TSH, free T4 and gender. Graves' orbitopathy (GO), using Clinical Activity Score (CAS), Group 1 had CAS 0 in 72 patients, CAS 1 in 16 patients, CAS 2 in 16 patients, CAS 3 in 6 patients, CAS 4 in 5 patients, CAS 5 in 2 patients, CAS 6 in 2 patients and CAS 7 in one patient. In the other hand the Group 2 had the fowling distribution of CAS: 0 in 125 patients, CAS 1 in 35 patients, CAS 2 in 17 patients, CAS 3 in 10 patients, CAS 4 in 3 patients, CAS 5 in one patient and no patients with CAS greater than 5 ($p < 0.02$). The CAS in Group 1 was higher (0.958 ± 0.019) than in and Group 2 (0.607 ± 1.01; $p < 0.005$). The thyroid volume, measured by US was classified according to volume and gender. Class A represents patients with goiters < 14 ml in female and < 18 in male; Class B denotes goiters between 15-21 ml in female and 19-27 ml in male; Class C represents goiters between 21-35 ml in female and 28-45 ml in male and Class D goiters > 35 ml in female and > 45 ml in male. The distribution in Group 1 was 30% class A, 22% class B, 26% class C and 22% class D, whereas Group 2 had smaller goiters and the following distribution: 34% class A, 28% class B, 23% class C and 15% class D ($p < 0.05$). **Conclusion:** Our data showed that there were significant changes in these 30 years in GD clinical presentation. Currently most of the patients display a mild forms of GO and smaller goiter. These findings may the result of early diagnosis, more access to specialized healthcare and iodide salt intake.

56703 COMPARISON BETWEEN TRAB AND TSI MEASUREMENT IN 75 PATIENTS ADMITTED AT A REFERENCE LABORATORY IN BRAZIL

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Introduction: Graves' disease (GD) is characterized by the presence of stimulatory (TSAb/TSI) and blocking antibodies (TBAb) in variable titers. TRAb receptor assay measure TSAb and TBAb; TSI receptor assay measure only TSAb. These assays shows close correlation with the results of radioiodine uptake (RAIU), thyroid hormone levels, Graves' ophthalmopathy and GD relapse, bing biologic markers for diagnostic and therapeutic purposes of GD. **Objectives:** To compare TRAb and TSI performance in patients submitted to thyroid evaluation. **Patients and methods:** A cross-sectional study was performed at a reference laboratory in Brazil. Patient data were collected from case notes and included age, gender and medication history. Results of TRAb and TSI were compared. Serum TSAb was analyzed using an Immulite 2000 TSI chemiluminescent assay, Siemens. According to the manufacturer subjects without GD score lower than 0.55 IU/L. Serum TRAb was measured on the Roche electrochemiluminescence immunoassay Elecsys. According to the manufacturer subjects without autoimmune disease score lower than 1.75 IU/L. Pearsons' correlation was applied to evaluate correlation between TRAb and TSI results. **Results and discussion:** Seventy five patients, 61 female, for whom TRAb measurement had been requested also had the TSI measured and were included in the study. Mean age was 42,4 ± 15 years. Forty nine (65 %) patients showed positive TRAb and the same number showed positive TSI. Five patients (6 %) presented negative TRAb and positive TSI; 6 (8 %) presented negative TSI and positive TRAb. Four (80 %) of the five patients with positive TRAb and negative TSI presented history of hyperthyroidism treatment and current hypothyroidism, suggesting that high TRAb levels could be due to blocking antibodies. Five (83%) of the six patients with positive TSI and negative TRAb presented clinical history of treatment of hyperthyroidism; all presented normal T4 levels and elevated TSI levels (mean 1,22 UI/L, range 0.637-2,08 UI/L), signalizing that these patients may present a greater recurrence risk of the disease. As expected, correlation between TRAb and TSI was strongly positive (r = 0,82). **Conclusion:** Our experience with the TSI dosage is still limited, but we can conclude the incorporation of the test into routine clinical use will improve GD management through its particular value in assessing disease activity and severity and in providing prognostic value with regard to treatment.

56711 CORRELATION OF CLINICAL ACTIVITY SCORE BETWEEN ENDOCRINOLOGIST AND OPHTHALMOLOGIST IN PATIENTS WITH GRAVES' ORBITOPATHY

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Introduction: Graves' orbitopathy (GO) is the most common extra-thyroid manifestation of Graves' disease. Its diagnosis and management requires multidisciplinary group. The consensus of the European Group on Graves' Orbitopathy (EUGOGO) recommends the use of the Clinical Activity Score (CAS) for the assessment of patients with GO. Both ophthalmologists and endocrinologists use this tool. There are no studies in our country that evaluate its application. **Objectives:** To perform a correlation of the value of CAS estimated by the endocrinologist and the ophthalmologist in a multidisciplinary group that manage patients with GO. **Method:** Prospective study. The CAS was independently applied to patients with GO by an endocrinologist and an ophthalmologist. The Kappa index is calculated for the correlation between observers. The STATA 10 was used for the analysis. **Results:** We included 38 patients. 75,7% (n = 28) were female. The average age was 40,8 (range 17-68) years. 39,5% (n = 15) presented active OG defined by CAS > 3. We found a positive correlation between the CAS calculated by the endocrinologist and the ophthalmologist ($R2 = 0.95$, $p < 0.01$). There was a 79% concordance. The Kappa index was 0.73 with $p < 0.01$. **Conclusions:** An adequate correlation was found in the CAS applied by endocrinologist and ophthalmologist in patients with OG.

56716 FASTING GLYCEMIA IN GRAVES' OPHTHALMOPATHY: SEVERITY SCORE IN CAS PRESENTATION?

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Introduction: It is known that thyroid hormones, among their various functions, also regulate carbohydrate metabolism, which favors glucose intolerance or even *diabetes mellitus* (DM2) among patients with hyperthyroidism. Literature data point to an interaction between vascular disease secondary to DM2 and the severity and frequency of ophthalmopathy in Graves' disease. **Objective:** To evaluate fasting glycemia (FG) in patients with Graves' ophthalmopathy (GO) and to correlate them with the value of the CAS (Clinical Activity Score), in an initial consultation, observing frequencies of glycemia greater than 100 mg/dL, in different classes of CAS. **Methods:** Ten women with a mean age of 51.5 ± 16.9 (med 52.5; 16-77) with GO were randomly selected. All of them were initially checked with fasting glycemia, TSH, FT4, TRAb, and CAS-evaluated. The Spearman Non-parametric Correlation Test was applied to the CAS with the variables FG, TRAb, TSH and FT4. The same test was applied to FG with the variables TRAb, FT4, TSH and age. We also analyzed the frequency of FG greater than 100 mg/dL in the different CAS evaluations found in the studied group. **Results:** The CAS evaluation found, per patient, showed CAS 0 in 1; CAS 1 in 3; CAS 2 in 2; CAS 3 in 3; And CAS 4 in 1. The fasting glycemia distribution showed that 2 of the 3 patients with CAS 3 presented FG greater than 100 mg/dL – 107 and 139 mg/dl; And for CAS 4, the only patient, also presented glycemia greater than 100 mg/dL – 114 mg/dL. Carriers of CAS 2 maintained their GJ below 100 mg/dL. Of the patients with CAS 1, two showed GJ greater than 100 mg/dL – 104 and 115 mg/dL. For the CAS 0 patient the fasting glycemia was less than 100 mg/dL. The mean FT4 was 2.8 ± 2.0 (med 1.9, 7.8 to 7.8) ng/dL, RV: 0,93-1,7 ng/dL; for TSH the mean was 0.26 ± 0.8 (med 0.005, 0.001 to 2.56) mcUI/mL, RV: 0,27-4,2 mcUI/mL; for TRAb values the mean was 15.8 ± 15.6 (med 9.7, 3.1 to 48.4) UI/L, RV: < 1,75 UI/L; no correlation was significant by the applied test. **Conclusion:** Although the sample size is small, and no significant correlation was found between FG and CAS, in the initial presentation of the GOs studied, the assessment of fasting glycemia with DM2 investigation, if necessary, should be part of the laboratory routine of these patients. As high glycemia favors inflammatory processes, a more effective glycemic control should be considered in patients with GO.

56569 I^{131} + PERCUTANEOUS INJECTIONS OF ETHANOL WITH LIDOCAINE IN THE TREATMENT OF HYPERTHYROIDISM ASSOCIATED WITH SECONDARY HYPERPARATHYROIDISM IN ESRD PATIENTS

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Introduction: Hyperthyroidism may be associated with hyperparathyroidism. Secondary hyperparathyroidism is manifested by a disorder of the metabolism of calcium, phosphorus, and bone tissue production, caused by increased parathyroid hormone (PTH) function and secretion. We report three cases of nodular hyperthyroidism in female patients aged 38, 42 and 49 who had secondary hyperparathyroidism undergoing hemodialysis who were treated in Cedin with oral ^{131}I and multiple percutaneous ethanol and lidocaine injections under ultrasound. **Objective:** To treat hyperthyroidism with ^{131}I and secondary hyperparathyroidism in ESRD patients with lidocaine and ethanol percutaneous injections. **Material and methods:** During 2016, three patients, one masculine and two feminine of 32,49 and 62 year old presented solid thyroid nodules on the ultrasound with hyper uptake on thyroid scintigraphy with Tc^{99m}. Parathyroid studies revealed hot areas with Tc^{99} with MIBI. ^{131}I in solution was used to treat the patients and ethanol injections with previous administration of lidocaine. **Results:** Four months post-therapy with ^{131}I at doses of 14,15 and 17 mCi showed remission of hyperthyroidism and multiple percutaneous injections of alcohol with previous lidocaine as local anesthesia under sonography every 10 days allowed renal transplantation. Laboratory studies showed a serum calcium of 12.5 mg (8.5-12.5 mg/ml), a PTH of 1,500 mg (VN 15-65 mg/dl). Pre therapy the TSH was 0.001 mIU/L (0.4-4.0), T3 was 220 pg/ml (40-120 pg/ml); FT4 from 5.23 pg/ml (1.2-2.0 pg/ml), TPOab 558.0 U/ml (inferior to 35 U/ml) and TGab and 834.0 U/ml (inferior to 40 UI/ml), TRAb: 1.58 UI/L (VN inferior a 1.75 UI/L). After both therapies the PTH mean was reduced to 254 mg, TSH increase to 8.87 pg/ml, T3 decreased to 60.0 pg/ml, FT4 decreased to 1.07, calcium decreased to 9.5 mg/ml, TPOab: 184.0 U/L and TGab 215.0 U/L. A dose of 100 mcg/d of L-thyroxine was given to achieve normalization of TSH at 4 months post ^{131}I therapy. **Conclusion:** Hyperthyroidism and hyperparathyroidism may be affect to the same patient with ESRD and can be treated with ^{131}I + ethanol injections with lidocaine under ultrasonography.

56697 RECURRENCE OF OPHTHALMOPATHY AFTER CURE OF GRAVES' DISEASE

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Introduction: Graves' ophthalmopathy is a disease that affects the orbits, being characterized by inflammation, congestion, hypertrophy, fat fibrosis and orbital muscles, causing a volumetric increase of the muscles. **Case report:** M.C.C.S., 56 years old, female, Caucasian, in treatment of hypothyroidism after total thyroidectomy performed in 2004 due to the diagnosis of hyperthyroidism and Graves' ophthalmopathy. In July 2015, in routine consultation, she was using levothyroxine 112 mcg and complained of restlessness, nervousness and insomnia. Physical examination showed bilateral asymmetric proptosis, predominantly to the right, preserved ocular extrinsic motility, without inflammatory signs. The following laboratory tests were requested (07/24/15): TSH: 0.84 µUI/mL (VR: 0.4 to 4.2 µUI/mL), free T4: 1.26 ng/dL (VR: 0.7 a 1.48 ng/dL). Computed tomography of the orbit (06/07/15): thickening of bilateral extrinsic ocular musculature of heterogeneous appearance. Bilateral exophthalmia, more accentuated to the right. An ophthalmologist evaluation was requested. In October 2015, she had ocular pain, diplopia, conjunctival hyperemia, 22 mm proptosis on the right and Clinical Activity Score (CAS > 5) with normal thyroid function. The patient was medicated with prednisone 80 mg/day. After resolution of the diplopia, the patient suspended the medication on its own, not completing the appropriate treatment. In a return visit on 12/29/15, she complained of ocular pain, diplopia, visual turbidity and presented the following laboratory tests (12/21/15): TSH: 0.2 (0.34 - 5.6), free T4 1.26 (0.7-1.48). The levothyroxine dose was adjusted to 100 mcg and pulse therapy was prescribed with methylprednisolone 0.5g (bolus weekly) for 6 weeks and then 0.25g; showing improvement of the patient's complaints. During 2016, the patient did not present worsening of Graves' ophthalmopathy. The patient is being followed by the services of endocrinology, ophthalmology and neurology due to the application of botulinum toxin in the right eyelid for it's better occlusion. **Discussion:** The reported case and current medical literature show the possibility of recurrence of ophthalmopathy, even in Graves' disease remission. It has been found in the literature that thyroid-associated ophthalmopathy can occur in the absence of Graves' disease in 10% of patients, and most of these individuals exhibit hypothyroidism. **Conclusion:** It is a case of recurrent ophthalmopathy years after Graves' disease cure.

56725 SUBCUTANEOUS ABSCESS IN CERVICAL TOPOGRAPHY IN A PATIENT WITH SERIOUS DISEASE IN REFERENCE: CASE REPORT

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Acute thyroiditis, also called acute or infectious suppurative thyroiditis, is a rare condition. In general, it has bacterial origin (70% of cases). It presents as differential diagnosis the subacute granulomatosa thyroiditis, lymphocytic thyroiditis and other infectious processes in thyroid topography. We report a case of a 32-year-old female patient with Graves' disease in remission. The patient attended the outpatient clinic, reporting an increase in goiter volume, in addition to local hyperemia and pain in the same topography for one month. She sought medical attention, and the hypothesis of an abscess was raised and she started treatment with cephalexin. He denied fever. It evolved with improvement of local pain and reduction of goiter volume. At the time of the consultation, he referred to heat intolerance, adynamia and hyporexia. She was on Tapazole 20 mg/day. She was hospitalized for a better investigation of the condition. Admission examinations did not show leukocytosis but showed increased CRP. Initiated antimicrobial coverage with Cefazolin. Patient did not present fever and evolved with spontaneous drainage of purulent secretion. Ultrasonography showed an image compatible with abscess. Contrast cervical tomography revealed a septate collection of thickened walls, extending in the anterior median line, starting immediately below the thyroid cartilage until the cervico-thoracic surgery, at the sternal furcula, measuring 6.6 x 3.8 x 9 cm. Surgical drainage and biopsy were performed. The culture of the material was negative for pyogenic germs and the study of alcohol-acid-resistant bacilli was negative. The patient evolved with clinical improvement, decreased CRP and no relapse of the suppurative collection. This case is important because it presents subacute evolution and with little systemic manifestation for an abscess. In addition, it leads us to discuss the possible differential diagnoses for abscess in cervical topography, such as the infected thyroglossal duct cyst, tuberculosis and subacute granulomatous thyroiditis.

56656 THIONAMIDE – INDUCED AGRANULOCYTOSIS: CASE SERIES FROM A PERUVIAN HOSPITAL

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Introduction: Agranulocytosis represents the fearest and rare complication of treatment with thionamides (rate 0.11%-0.35%). Most events occur within 90 days of treatment. Associated risk factors are: age, re-exposure and dose ≥ 30 mg/dl. **Objective:** To describe general characteristics of in-patient thionamide-induced agranulocytosis (TIA) of a third level hospital. **Methods:** Descriptive-retrospective study, type series of cases. We reviewed medical records of patients diagnosed with TIA between 2009-2017. Demographic, management (dose, frequency, re-exposure) and hospitalization data were recorded, creating a database and subsequent analysis in SPSS v18. Central tendency and dispersion measures were determined. **Results:** We found 11 cases of TIA, all of them Grave's disease (100%). The mean age was 32.6 ± 12.2 years and 64.6% being female. Disease duration was 7 ± 5.8 days. Most frequent presenting symptoms were fever (90.9%) and odynophagia (81.8%). At admission, SBP 110.2 ± 17.3 mm Hg, DBP 64.5 ± 12.1 mmHg, heart rate 110.3 ± 15.9 bpm and T° 37.9 ± 1.1 C° were recorded. On thyroid exam, all with diffuse goiter, 72.7% with WHO classification II and estimated weight of 74.6 ± 18.1 gr. In laboratory results, TSH 0.03 ± 0.4 mUI/ml, T4f 2.66 ± 1.6, leukocytes 1227.9 ± 2068/mm^3 and granulocytes 241.6 ± 151.7/mm^3. Methimazole mean dose was 28.2 ± 10.8 mg/d and all received 386.2 ± 716.7 days prior to the event. In the management, 81.8% was treated with lithium carbonate, 18.2% Lugol and all (100%) colony-stimulating factor (FSC) for 6.3 ± 2.7 days associated with beta-blockers, achieving resolution in 7.6 ± 2.7 days. **Discussion:** Grave's disease (GD) is the most frequent cause of hyperthyroidism, with high rates in female patients, iodine-sufficiency areas and young adults (30-60y), explaining higher thionamides use and adverse effects in these groups. Dose ≥ 30 mg/dl carry a higher TIA risk, however, in recent studies risk increases from 25 mg/dl. 85% of TIA's occur within 90 days of treatment, but may occur up to 12 months. Presenting symptoms were similar to previous reports. On exam, tachycardia could be secondary to fever or to decompensated hyperthyroidism, corroborated by finding in hormonal test. Lithium carbonate, beta-blockers and FSC were used in most cases, Lugol being the less used. Resolution time was lower than previous local report probably by standardization of FSC use.

56607 CONSUMPTIVE HYPOTHYROIDISM: CASE REPORT OF HEPATIC HEMANGIOENDOTHELIOMAS SUCCESSFULLY TREATED WITH VINCRISTINE AND SYSTEMATIC REVIEW OF THE SYNDROME

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Introduction: Consumptive hypothyroidism syndrome (CHS) is a severe form of hypothyroidism due to the high expression of thyroid hormone-inactivating enzyme type 3 deiodinase (D3) in tumoral tissues. Although the CHS has been initially noted in neonates and children with vascular tumors, it is not restricted to this age group nor this kind of tumors. To date, there is no summarized data of CHS on literature. **Objectives:** Describe one case of CHS and provide a summarized description of the cases reported to date. **Methods:** A case of CHS cured after treatment of hepatic hemangioendotheliomas is reported. A systematic review of the databases PubMed/Medline and Embase, using the term "Consumptive AND Hypothyroidism" was performed. From the 33 selected references, we extracted 42 case reports of CHS. A summarized description of the CHS clinical characteristics, treatments and outcomes was provided. **Results:** Here, we present the case of a seven-month-old female patient with a diagnosis of massive hepatic hemangioendotheliomas. After treatment with high doses of thyroid hormones, our patient started tumor-directed chemotherapy with vincristine. The tumor displayed excellent response, and euthyroid status was regained. Our systematic review summarizes 42 CHS cases reported: 36 children and 6 adults. The laboratory profile at diagnosis displayed high TSH and low T4 and T3 serum levels. The serum reverse T3 (rT3) and D3 activity levels were high in all patients tested. In children, 97% were vascular tumors, with only one case of a solid tumor – a fibrosarcoma; whereas in adults, 33% were vascular tumors, 33% fibrous tumors and 33% gastrointestinal stromal tumors. The conservative treatment was predominant in children, while in adults all cases were treated with surgery. Death occurred in 16% of children and 33% of adults. **Conclusion:** The CHS is a rare form of hypothyroidism, that occurs in children and adults, usually linked to hepatic vascular tumors. The condition is associated with high lethality. Prompt diagnosis and institution of appropriate high dose thyroid hormone replacement and tumor-directed therapy are the keys to optimize outcomes.

56712 HYPOTHYROIDISM REDUCES AUTOPHAGY AND MODULATES SIGNALING PATHWAYS TRIGGERED BY ENDOPLASMIC RETICULUM STRESS IN SKELETAL MUSCLE

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Introduction: Autophagy is a physiological process through which cells degrade and recycle their long-lived proteins and organelles, ensuring cell homeostasis and function. Either autophagy hyperactivation or inhibition may compromises muscle homeostasis and led to muscle loss. Decrease in autophagy results in accumulation of obsolete structures and homeostasis disruption, which causes endoplasmic reticulum (ER) stress. Both disrupted autophagy and ER stress are related to several diseases. Thyroid hormones play a crucial role in muscle homeostasis and function and muscle loss and weakness are associated with hypothyroidism. **Objectives:** Investigate the influence of hypothyroidism state in autophagy and ER stress. **Methods:** Male Wistar rats were divided in two groups: euthyroid (EU; n = 8) and hypothyroid (HIPO; n = 8), induced by methimazole (0.03%) diluted in drinking water (approved by UFF's Ethics Committee #757/2016). After 21 days of treatment, animals were euthanized and soleus muscles were weighted and frozen for analysis. T3 and T4 serum level were analyzed by radioimmunoassay and protein expression was analyzed by Western Blot. Statistical analysis was performed using Student's Test-t. **Results:** Undetectable levels of T3 and T4 were found in HIPO group. Soleus muscles of these animals showed lower expression of the autophagy markers analyzed: Beclin ($p < 0.05$); Atg5 ($p < 0.001$) and LC3II/I ($p < 0.001$). These findings suggest that autophagy is reduced by hypothyroidism state. Regarding the ER stress markers, phosphorylation of eIF2α, usually triggered by ER stress, was found diminished in HIPO group ($p < 0.05$). Reduced phosphorylation of eIF2α might contribute to maintain high levels of D2, since phosphorylation of eIF2α induced by ER stress is involved in decrease in D2 activity. Also, lower levels of p-eIF2α might contribute to the reduced autophagy, as it activates a transcription factor associated to autophagy-related genes expression. Interestingly, CHOP protein expression, an ER stress marker, was found increased in HIPO group ($p < 0.05$), suggesting the activation of other ER stress pathways. Therefore, the ER stress might be a consequence of reduced autophagy. **Conclusion:** Hypothyroidism reduces autophagy in skeletal muscle, which might induce ER stress through eIF2α-independent pathways. In addition, diminished p-eIF2α may contribute to the reduced autophagy phenotype observed in the hypothyroidism.

56625 INSIDE GENOMIC FOXE1 VARIATIONS IN THYROID DYSGENESIS: POLYMORPHIC LENGTH OF ALANINE STRETCH WAS ASSOCIATED TO ECTOPY AND HIPOPLASIA

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Forkhead box E1 (FOXE1) is a thyroid specific transcription factor involved in the maintenance, differentiation and development of the thyroid gland. Thyroid dysgenesis is the most common cause of congenital hypothyroidism (CH) and results from migration defects of the developing gland during embryogenesis. Up to now gene mutations have been identified in only 5% of the TD patients. The objective was to investigate FOXE1 genomic variants in CH patients with thyroid dysgenesis. FOXE1 genomic variants were investigated in the blood DNA samples from 29 unrelated TD patients from Bahia, Brazil, diagnosed with CH during neonatal screening (12 ectopia, 11 hypoplasia and 6 agenesis). Expanded whole exome sequencing that included 5 UTRs and 3 UTRs was performed with Illumina NextSeq 500 platform. Only two non-synonymous single nucleotide variants (SNVs) and 1 insertions/deletions (indel) were identified in the FOXE1 exon as well as 12 SNVs (6 new) in 5UUTR, 11 SNVs in 3UUTRs and 14 intergenic alterations (between XPA and FOXE1 genes). Two SNVs were of interest. The rs1867277 (c.-2283 G>A) located in FOXE1 promoter, previously observed as a casual variant in thyroid cancer and able to modulate gene transcription. The allelic frequency of this SNV was similar to control databases (A: 34%). The indel rs71360530 is an exonic stretch with 14 alanines. The 14/14 genotype was previously associated with increase risk of TD, particularly with ectopia, and with reduce expression of FOXE1 gene. In this study the 14/14 genotype was the most frequent (14/14 = 45%; 14/16 = 24% 16/16 = 31%) and was associated with ectopia and hypoplasia ($p = 0.016$). In conclusion, no mutations were identified in the exon, UTRs and intergenic sequences of FOXE1 gene in the 29 thyroid dysgenesis patients. Our data reinforce the genetic susceptibility to ectopy and hypoplasia of the 14/14 genotype of the polyalanine stretch in TD.

56621 INVESTIGATION OF GENOME VARIANTS WITHIN MICRORNA TARGET SEQUENCES IN THYROID DYSGENESIS

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MicroRNAs are small RNAS that regulate gene expression in a posttranscriptional sequence-specific manner. The have been involved in different biological process, including development. Thyroid dysgenesis (TD) is the most frequent cause of congenital hypothyroidism that occurs due to developmental defects. Up to now only 5% of the cases were associates to gene mutations. The aim of this study was to investigate the presence of single nucleotide variants sequence (SNVs) and insertions/deletions (indels) within 3MUTRs target regions of miRs in genomic DNA of thyroid dysgenesis patients. The candidate gene approach was adopted, thus the conserved miRNA target sites of miR-1-3p, miR-1-5p, miR-15a-3p, miR-15a-5p, miR-17-3p and miR-17-5p of 178 candidate genes possibly associated with the development of the thyroid gland were investigated. Expanded whole exome sequencing that included 5UUTR and 3UTR sequences of blood DNA of 18 patients with thyroid dysgenesis (TD) was performed. miR1 and miR15 were included because they were previously identified as differential expressed in thyroid dysgenesis by our group and miR17 was also associated to thyroid development by others. The alterations were analyzed with PolyMIRts, miRanda and TargetScan database. The SNVs and indels absent in the dbSNp database, with frequency < 0.001 in the 6.5 exome and not present in the 3U UTR of 18 Brazilian control subjects genome were selected. Bioinformatics analysis identified 105 different SNVs in 39 candidate genes, 74 of them were unique among patients while 31 were identified in several patients and belonged to 3 genes: BGN, HLA-DQB1 and EGR1. At all, 26 indels in 21 genes were also detected, 18 of the were unique among the patients. To evaluate the significance of alterations, it was verified if the 105 SNVs and the 26 indels located in conserved seed sequences of selected microRNAs. Only two SNVs located in the miR-17-3p target sequence of HLA-DQB1 gene, however this gene belongs to the major class II histocompatibility complex (MHC II) with an important role in immune system and autoimmune thyroid disease also. In conclusion none of the identified SNVs and indels in the target sequence of the selected miRs and genes could be associated with TD. A complete study is underway to verify the involvement of these and other microRNAs with the genetic variants within the seed sequences in the expanded exome of TD patients.

56626 INVESTIGATION OF GENOMIC VARIATIONS ASSOCIATED WITH THYROID DYSGENESIS

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Thyroid dysgenesis (TD) is the most common cause of congenital hypothyroidism (CH) affecting about 85% of cases. However, genomic variants in candidate genes, known to be involved since the early stages of thyroid development, have been identified in only 3% of patients. With new sequencing technologies, new genes have been associated with TD, allowing a greater understanding of the genetic mechanisms of the thyroid formation. The aim of our study was to investigate genomic variants associated to TD. This study included 17 unrelated Brazilian patients from Bahia state, diagnosed with CH in neonatal screening (6 ectopies, 6 hypoplasias and 5 agenesis). The whole exome and UTR regions sequencing of all patient s blood DNA was performed using Illumina NextSeq 500 platform. The candidate gene approach was adopted in this analysis. Thus the single nucleotide variants (SNVs) and insertion/deletion (indels) selection criteria were: non synonymous, not present in the exome of 6 controls individuals, present in 178 candidate genes that were already associated with thyroid development and function, present in exonic region and not described in databases. The Condel platform was used to verify possible deleterious effects on the protein. This analysis identified 23 SNVs in candidate genes while non indels were selected. These SNVs were present in the genome of 13 patients and 4 of them were observed in more than one patient. However, no correlation between the presence of this 4 recurrent alterations and the clinical and phenotype characteristics of patients was observed. Condel platform indicated a possible deleterious action of the SNVs presented in HADHA and TBX1 genes identified in heterozygosis in two ectopic patients. The HADHA gene participates in mitochondrial function and it has been demonstrated that T3-mediated ATP production is dependent on HADHA. This gene is highly expressed in thyroid tissue. TBX1 is a transcription factor involved since early thyroid embryogenesis, determining the correct size and position of the gland, is haploinsufficient and is considered the major candidate to DiGeorge syndrome. In conclusion we identified two new sequence alterations in the genome of TD patients. Only functional analysis will confirmed the association of these mutations with TD.

56577 PSEUDOMALABSORPTION OF LEVOTHYROXINE – SUCCESSFUL TEST TO CONFIRM THIS DIAGNOSTIC CHALLENGE

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Case presentation: We report the case of a 39-year-old woman who was thyroidectomized because of a multinodular goiter. She remained euthyroid on LT4 (137 mcg/d) during 5 months after surgery. Since then, serum TSH fluctuated between 21.3 and 70.5 mIU/L, despite high doses of LT4 (up 500 mcg/d; 7.24 mcg/kg) and ascorbic acid. All possible causes of malabsorption (MA), drug and dietary interactions were ruled out. Though the patient denied low compliance with LT4, a personal history of child abuse and drug addiction led us to suspect a psychological disturb. To confirm pseudomalabsorption (PMA), a close supervised absorption test with a fasting oral 1000 mcg LT4 single dose (LT4SD) was performed. The test results showed a decrease in TSH levels (27.1%) and a peak elevation of T4 (141.3%) and FT4 (174%) 2 hours post LT4 ingestion. We supervised weekly LT4SD intake for 6 weeks. Before each weekly dose, TSH and T4/FT4 were measured at 0A; 60; and 120; after LT4 intake. The patient remained euthyroid since the 3rd week (TSH: 2.99 mIU/L T4: 12.2 mcg/dL and FT4: 0.95 ng/dL), confirming PMA. Neither symptoms nor side effects were observed. **Discussion:** Some patients remain hypothyroid, despite being on therapy with high LT4 doses. The most common cause of this therapeutic failure is patient s non-compliance. An intentional lack of compliance should be considered a psychological disorder. This represents a challenge due to deficient diagnostic processes, patient denial and difficulties in management. Variable hormonal levels, also including euthyroid periods with the same replacement LT4 dose, suggest PMA. Differential diagnosis with MA and other biological causes must be taken into account, though discarding them requires multiple and complex diagnostic studies. Furthermore, LT4 intake with food, dietary fibers or drugs must be interrogated. A simple test that can demonstrate appropriate improvement of thyroid function tests 2 h after an oral high LT4SD intake could be initially performed to rule out a true MA. **Final comment:** Patients with emotional disturbs who are receiving high LT4 doses with variable TSH levels should undergo testing for PMA. An oral 1000 mcg LT4SD supervised test could be useful as initial test to confirm it, though it needs clinical validation. The observation of a rapid improvement in the thyroid function tests confirmed the diagnosis of nonadherence to treatment and allowed the beginning of a psychological treatment in our patient.

55901 REFRACTORY HYPOTHYROIDISM: A CLINICAL CHALLENGE

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Case: 40-year old female with hypothyroidism due to total thyroidectomy because of thyroid carcinoma presented with refractory clinical hypothyroidism despite high doses of levothyroxine (LT4; 300 mcg = 2, 54 mcg/kg/weight). She declared regular use of medication and denied concomitant use with other drugs or foods. She was quite symptomatic during medical exam, with slurred speech, slow thought and muscle weakness. Laboratory tests showed TSH = 126 mIU/L, T4L = 0, 6 ng/gl. The patient was admitted and initiated clinical investigation into possible causes of malabsorption. She underwent an endoscopy which showed pangastritis and duodenitis with bleeding areas suggestive of intestinal parasite. Also, she underwent a biopsy which was *Helicobacter pylori* positive and had no other findings. Both Anti-Endomysial and Anti-transglutaminase antibodies were negative for celiac disease. Finally, she performed an oral test overload with 1000 mcg of LT4 and after 4 hours dosed the free T4 (FT4) whose result was 26 mUI/l. She was discharged with reinforcement of the advise on the correct use of LT4 with further reduction of dose to 250 mcg/day. **Discussion:** Current guidelines recommend treatment of hypothyroidism with LT4 at least 30-minute morning fasting and an initial dose of 1.6 to 1.8 mcg/kg/weight. In most cases, the treatment is well tolerated and effective when properly carried out. Unsatisfactory clinical and laboratory control, despite the use of high doses, is rare. In this situation, causes of malabsorption, drug interactions and poor adherence to treatment should be excluded. For differential diagnosis, doctors can use the overload oral test with 1000 mcg of levothyroxine. **Final comments:** Overload oral test with LT4 is useful in cases of refractory hypothyroidism and it should be done after ruling out other causes.

56702 REFRACTORY HYPOTHYROIDISM TO ORAL LEVOTHYROXINE REPLACEMENT

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Introduction: Refractory hypothyroidism to oral levothyroxine replacement consists of the presence of elevated TSH despite increasing replacement dosages above 2,5 mcg/kg/day. Common causes include poor adherence to treatment and interactions between levothyroxine and other drugs or foods. Organic causes also need to be assessed. **Objective:** To evaluate the causes of refractory hypothyroidism to oral levothyroxine replacement in follow-up patients at the Department of Endocrinology and Metabolism of Clinical Hospital from Federal University of Paraná (HC-UFPR). **Patients and methods:** Retrospective study of case reports, approved by the HC-UFPR Ethics Committee. We selected patients with hypothyroidism on levothyroxine replacement above 2,5 mcg/kg/day. Pregnant women and patients with coronary artery disease were excluded. Evaluation of drug interactions, organic causes and poor adherence were done, including psychiatric evaluation. **Results:** fifteen patients were initially selected. One patient was excluded for stable angina, one for breast cancer treatment, one for non-contact and two for dose adjustment below 2,5 mcg/kg/day on the first interview. Ten patients remained, of which 80% were women, with a mean age of 44 years old, using a median levothyroxine dose of 5 mcg/kg/day (3,21-29,26) and median TSH level of 8,08 mU/L (2,45-53,77). Possible drug interaction was observed in 6 patients. All patients received empiric treatment for intestinal parasitosis. None had a history of previous gastrointestinal surgery. Organic causes evaluation showed four cases of *H. pylori* infection, four cases of lactose intolerance and one case of celiac disease. Psychiatric evaluation showed three patients with depression, two with bipolar disorder and one with probable cognitive impairment. Finally, all subjects underwent oral levothyroxine intake with 1000 mcg. Only one patient did not absorb the medication and had no identified cause for refractory hypothyroidism. Among the nine patients with positive test, one had an isolated diagnosis of depression, one of lactose intolerance and one of *H. pylori* infection; the other six patients had more than one cause for refractory hypothyroidism. **Conclusion:** refractory hypothyroidism is a less prevalent condition, with a multifactorial etiology observed in most of the patients in this study (60%). Poor adherence remains a predominant factor, being related with psychiatric disorders in 50% of the cases.

56684 THYROID ECTOPIC TISSUES: SCREENING OF ALTERATIONS THOUGH EXPANDED EXOME ANALYSIS

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Congenital hypothyroidism (CH) due to thyroid dysgenesis (TD) occurs with an incidence of 1/4,000 live births. The gland's incorrect placement, or ectopic thyroid, is the most common defect during embryologic development and affects 75% of TD patients. As genomic mutations have been identified in only 3% of cases, new sequencing technologies can bring greater knowledge of the genetic mechanisms of the disease and thyroid formation. The aim of this study was to investigate somatic variants associated to TD in thyroid tissues. Tissue samples of ectopic thyroid from two patients were analyzed. The whole exome and UTR regions sequencing of patient's tissue DNA was performed using Illumina NextSeq 500 platform. The candidate gene approach was adopted in this analysis. The single nucleotide variants (SNVs) and insertion/deletion (indels) selection criteria were: non synonymous, not present in the exome of 6 controls individuals, present in 178 candidate genes that were already associated with thyroid development and function, present in exonic and promoter regions and not described in databases or with prevalence < 1%. The Condel and Mutation Taster platforms were used to verify possible deleterious effects on the protein. This analysis identified 35 potential functional important SNVS in candidate genes but no indels. Only one SNV was detected in both samples. Condel and Mutation Taster platforms indicated a possible deleterious action of 6 SNVs in exonic region, 5 already described SNVs in: DUOXA1 and TG genes involved in T3 and T4 production and in thyroid dyshormonogenesis; KMT2C gene with monoallelic expression in TD, encodes a nuclear protein with histone methylation activity; CNTN6 found to be highly expressed in thyroid tissue encodes a neuronal membrane protein involved in cell adhesion. The other SNV was not described in databases, and localize in FCGBP gene, involved in thyroid cell division and migration and with monoallelic expression in TD. In promoter regions, 5 variants were identified in TEF, FZD1, THRA, ICK and FMR1 genes. In conclusion expanded exome analysis allow to identify genomic variants with deleterious potential in candidate genes for TD. Functional analysis will confirm the association of these SNVs found in ectopic thyroid tissue with TD.

56714 THYROID HORMONE REPLACEMENT EVALUATION IN BARIATRIC SURGERY POSTOPERATIVE PATIENTS

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Introduction: Insulin and leptin resistance presents in obesity seems to mediate TRH hypothalamic regulation in obesity patients. A raise in serum thyroid stimulating hormone (TSH) can be observed in obesity patients especially in class 2 and 3 individuals. Although bariatric surgery is effective to improve thyroid metabolism, there is a doubt about whether it can improve thyroid hormone replacement (THR) in hypothyroidism patients. **Objectives:** We evaluated THR in obese patients pre, 6 and 12 months after bariatric surgery. **Methods:** Levothyroxine dose per kilogram (LDK) of 10 patients submitted to bariatric surgery were analyzed pre, 6 and 12 months after surgery. Mean differences were analyzed using Wilcoxon test. THR values pre-operative, 6 and 12 months after surgery were correlated using Pearson test for correlations. All data were analyzed used IBM SPSS statistic 22. **Results:** Patients mean age were 46.2 years (±11.1) and all patients were woman. Preoperative body mass index were 48.7 kg/m^2 (± 8.5). Mean weight pre 6 and 12 months postoperative were respectively 125.8 kg (± 35.8), 88.7 kg (± 18.3) and 83.8 kg (± 15.0). There were a significant difference between pre and 6 months postoperative LPK (p = 0. 007) and 12 months (p = 0.005). LPK pre and postoperative was positive correlated after 6 months (r = 0.92; p = 0.001) and 12 months (r = 0.88; p = 0.001). **Conclusions:** Although weight loss may contribute for falls in TSH levels after bariatric surgery in obese patients it didn't happen in patients using TRH of our study. All patients needed a levothyroxine improved dosage per kg after surgery. There was a positive correlation in pre and postoperative doses of LPK.

IODINE DEFICIENCY

56559 CASSAVA FLOUR CONSUMPTION AND IODINE NUTRITION IN SCHOOLCHILDREN: A SURVEY IN BAHIA STATE, BRAZIL

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Introduction: Cassava (*Manihot esculenta Crantz*) is an important food source in many poor countries. This root contains cyanoglucosides which can aggravate iodine deficiency disorders (IDD). **Objective:** To analyze the impact of cassava flour consumption (CFC) among schoolchildren from public school in Brazil on urinary iodine concentration (UIC). **Methods:** Cross-sectional study conducted on 1,231 schoolchildren (ages between 6-14 years-old) from public school in Bahia. We evaluated anthropometric parameters, household food insecurity, UIC and CFC. **Results:** The prevalence of CFC was of 90.8%. The mean UIC was indicative of adequate iodine nutrition in both groups: group A (CFC positive) and group B (CFC negative) (203.29 ± 81.08 µg/L *vs.* 225.98 ± 76.59 µg/L, respectively). We found that the daily cassava flour intake did not significantly raised the risk of iodine deficiency (ID) (odds ratio [OR] = 1.43 [confidence interval (CI) 0.72-2.82]; p = 0.29), neither significantly protected against excessive iodine intake (EII) (OR = 0.70 [CI 0.39-1.26]; p = 0.24). The prevalence of iodine deficiency (ID) (12.6% *vs.* 8.9%) and EII (9.6% *vs.* 15%) did not significantly differ between both groups. **Conclusion:** The results of the current study suggest that the cyanides present in cassava flour have very little influence on iodine metabolism, which is probably justified by cassava processing methods.

55126 COMPARISON OF IODURIA VALUES AMONG RIBEIRÃO PRETO SCHOOLCHILDREN IN THE PRESENCE OF DIFFERENT IODINE CONCENTRATIONS IN THE INDUSTRIALIZED SALT CONSUMED – RIBEIRÃO PRETO, SP

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Introduction: In order to compare the ioduria of Ribeirão Preto schoolchildren, in 2015 we conducted a study (Anvisa Regulation: 15-45 mg iodine/kg industrialized salt) comparing the ioduria values of schoolchildren to those detected in a study conducted in 2010 (Anvisa Regulation: 20-40 mg iodine/kg industrialized salt). **Material:** We evaluated 289 schoolchildren of both sexes from 3 schools of different socioeconomic level previously studied in 2010 (300 schoolchildren): School 1: lower level; School 2 intermediate level; School 3: higher level). Ioduria values were significantly lower in School 1 (in 2010 and 2015) compared to Schools 2 and 3 (2010 and 2015). **Results:** Mean ioduria values were 221 µg/L in 2010 and 344.8 µg/L in 2015 and were statistically significant ($p < 0.0001$). Ioduria also showed statistically significant values among the schoolchildren of the 3 schools in 2010 and 2015 when the children were compared individually. In 2010, 55.2% of the samples showed ioduria values higher than 300 µg/L, indicating excessive iodine intake, and no cases of ioduria levels lower than 100 µg/L indicating iodine deficiency. In 2015, 32.2% of the ioduria values were higher than 300 µg/L and 10,9% were lower than 100 µg/L (8% in School 1 and 1% in School 2). No significant difference was detected when the ioduria values and thyroid volume were compared. However, in 2010 we did not detect the presence of an increased thyroid volume, while in 2015 we detected 29 cases of palpable thyroid (21 in School 1) and 18 cases of visible and palpable thyroid (13 in School 1). **Conclusion:** The reduced iodine concentration in industrialized salt consumed starting in 2013 led to a statistically significant reduction of mean ioduria values; there was a reduction of cases of excessive ioduria, although they continued to occur, indicating an increased iodine intake. Ioduria values lower than recommended were detected, indicating deficient iodine intake, a fact that was not observed previously. Thus, it is necessary to re-evaluate the ioduria of schoolchildren in order to detect a possible increase of cases of iodine deficiency in the presence of the new regulations and the possible repercussions of this finding on the thyroid function of the lower socioeconomic class. Acknowledgment to the Endocrinology Leage of Unaerp year 2015.

56657 QUANTITATIVE DETERMINATION OF IODINE IN COMMERCIAL FOOD-GRADE SALT IN BAHIA, BRAZIL: HIGH PREVALENCE OF UNDER-IODIZED SAMPLES

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Introduction: In 2001, the Thyromobil Project confirmed that schoolchildren in Brazil were receiving excessive iodine ingestion (EII) and close to 50% of all salt samples (collected at homes) contained more than 60 mg of iodine/kg of salt. In order to avoid EII, the levels of salt iodization were additionally reduced to 15-45 mg of iodine/kg of product in 2013. The WHO established that more than 95% of the sampled edible salt needs to be in accordance with national laws. Campos *et al.* (THYROID, 2016), in a subnational field work at state of Bahia, demonstrated that 12.3% of schoolchildren had a low (< 100 µg/L) urine iodine concentration (UIC) and 9.4% presented EII. More recently, the PNAISAL (National Survey for Iodination of Salt Impact Assessment) involved 18.864 schoolchildren, showing a prevalence of 10.4% for iodine deficiency (ID) and 44.6% for EII. Indeed, the collected mean salt iodine concentration (SIC) (n = 1.120) was 40,14 ± 2,72 µg/g, with 93.6% and 28.9% of samples containing more than 15 and 45 ppm, respectively. **Objective:** To assess SIC in commercial edible salts available in the local market at Bahia, Brazil. **Methods:** SIC was determined in duplicates by iodometric titration in which potassium iodate (KIO3) react in solution acid releasing iodine, which is titrated with sodium thiosulfate. Four type of salt were collected: Unrefined (UR) (gross and ground), Refined (R) and Himalayan. Data were stratified by level of SIC. **Results:** A total of 50 samples, from 30 most commonly available different brands (40 UR, 8 R, 1 Himalayan, 1 Unknown), being commercialized in different grocery stores from 28 different cities from Bahia, were purchased for the study. The overall mean SIC was 26.6 ± 16.3 mg/kg (range of 0 to 80.2 mg/kg), with a median of 26.8 mg/kg. 34% of samples showed SIC outside the recommended range (15-45 mg/kg): 13/50 (26%) and 4/50 (8%) were, respectively, bellow and above. The mean SIC were 23.7 ± 16.7, 30.8 ± 21.5, and 31.9 ± 5.2 mg/kg to UR ground (n = 30), UR gross (n = 10), and R salt (n = 8), respectively. Overall UR SIC was 25.5 ± 5.2 mg/kg *vs.* 31.8 ± 5.2 mg/kg in the R group ($p = 0.32$). All 13 (2 gross/11 ground) found insufficient iodized salt were UR type. Two samples presented 0 ppm of iodine. **Conclusion:** A non-uniform iodine content and high prevalence of unsatisfactory iodized samples were found. UR salt seems to be less iodized. Supervision by health authorities must continue. **Support:** Fapesb. Grupo WhatsApp Endocrinologia Bahia.

56568 URINARY IODINE EXCESS IN PREGNANCY ASSOCIATED WITH HYPOTHYROIDISM AND GESTATIONAL DIABETES IN PARAGUAY

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Introduction: The main indicator of the impact of iodination of human salt consumption is the urinary concentration of iodine which is useful in salt monitoring. The levels of urinary iodine concentration as well as TSH and glycaemia are important for monitoring diabetes and hypothyroidism in pregnancy. **Objective:** To determine the urinary levels of iodine and iodine in salt, glycaemia and TSH in 200 pregnancy from 15 to 37 years old, with a mean of 26 Z < at the Hospital San Pablo de Asuncion. **Material and methods:** During 2015, two hundred pregnant women were studied with urine samples to get the urinary iodine concentration, were also obtained salt samples from 100 grams of the salt consumption in their homes to determine iodine and from fasting blood glucose and 2 hours postprandial, TSH dosing were performed in all pregnant women. The determination of urinary iodine was performed according to the method of ammonium persulfate (Sandell-Kolthoff reaction. Modified Pine and Dunn).The data was obtained by means of statistical calculations. All the candidates were studied under authorized consent and according to ethical standards. **Results:** The pregnant women studied had a mean urinary level of 484 µg/L, the iodine salt content was 39.7 µg/L, and gestational diabetes was observed in 50% of pregnant women with a mean fasting blood glucose of 128 mg/dl: the 2 hours post prandial was 146 mg/dl. Hypothyroidism was observed in 50% (40.5% subclinical hypothyroidism, 9.5% overt hypothyroidism, TSH levels were considered normal in the first trimester TSH < 2.5 uUI/ml, 2nd and 3rd trimester TSH < 3.0 µUI /ml). All patients who presented higher levels of TSH were treated with levothyroxine sodium, fasting 75-125 mcg/day. **Conclusion:** To normalize iodine levels, it is necessary to decrease the amount of iodine in the salt. The recommendation is to insist on the monitoring of the adequate iodization of the family consumption salts and to continue with the monitoring and constant monitoring in sentinel sites divulging the importance of the adequate intake of iodine to the population. Subclinical hypothyroidism produces abortion and premature birth in pregnancy. Gestational diabetes may increase fetal hyperglycemia, free fatty acids, and fetal hyperinsulinemia, which may lead to increased fetal adiposity and acidosis, delayed pulmonary maturation, and neonatal hyperglycemia

MULTINODULAR GOITER

56638 AN UNUSUAL PRESENTATION OF GOITER: DOWNHILL VARICES

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Goiter is defined as an abnormal enlargement of thyroid due to several etiologies, commonly multinodular goiter. Hoarseness, cough, dysphagia, dyspnea and superior vena cava syndrome can be referred. Here we report a 60-year-old woman with anterior cervical enlargement for several years, worsening in the last year. She presented no symptoms of hypo- or hyperthyroidism, dyspnea or dysphagia. At physical examination her right thyroid lobe was very enlarged shifting left lobe and trachea. There were no dilated veins and superior vena cava syndrome were absent. Ultrasound revealed multiple solid, heterogeneous, confluent nodules at right lobe with an estimated volume of 223 cc. Isthmus and left lobe were normal. Thyroid function was normal. Iron deficiency anemia was detected with normal colonoscopy. Digestive endoscopy showed 2 medium-caliber varicose cords, with some tortuous red spots, located in the proximal third of esophagus, designed downhill varices related to superior cava obstruction. At vessels radiologic study, her mediastinal goiter shifted vessels from aortic arch, particularly brachiocephalic and left carotid arteries, with no stenosis. Right internal jugular vein had no stenosis but thyroid dislocated its middle and lower parts. Left internal jugular, subclavian and superior vena cava had normal calibers and filling. No malignancy of thyroid or lung were detected. Patient underwent to partial thyroidectomy with no complications. Downhill varices known as upper esophageal varices are associated with superior vena cava obstruction due to intrathoracic tumors and rarely due to goiter. Such varices may rarely be seen in the absence of superior vena cava occlusion and occurs with obstruction of inferior thyroid veins alone, secondary to benign or malignant thyroid neoplasms, thyroid surgery, or with internal jugular vein hypoplasia. Only 9 cases of bleeding secondary to downhill varices in thyroid pathologies (8 goiters and 1 carcinoma) were reported in the literature. However, up to 50% of a small cohort previously reported asymptomatic varicose veins due to goiter. Patients with intrathoracic goiter must be evaluated by digestive endoscopy, especially with anemia, as downhill varices could be a preventive source of an expected bleeding. Therefore, as thyroidectomy is highly effective to eliminate the cause of venous obstruction, the presence of esophageal varices must be included as an indication of precocious surgical treatment to large goiter.

56690 CERVICAL ABSCESS BY STRANGE BODY INTAKE, A CASE THAT MAY BE CONFUSED WITH SUPPURATIVE THYROIDITIS

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Case presentation: T.R.J., 65 years old, with multinodular goiter, had Graves' disease in 2012 with remission after use of Tapazole. The patient sought our service with cervical volume increase, starting 1 month and a half earlier. Palpable on the right side of the neck, associated with pain and fever. One week before she referred fish-spine intake and choking after ingestion of it. After consulting a doctor, two high digestive endoscopies were performed, which were normal, she used antibiotic for 10 days and showed improvement of fever but persisted with increased cervical volume and weight loss of 2 kg in this period. On ultrasonography, performed in our service, the patient had multiple nodules with a solid hypoechogenic dominate in the left lobe of 1.7 x 1.14 x 2.04, and another solid nodule, with a large central cystic area in the right lobe, isoecogenic of 2.9 x 1.8 x 1.5. At the time, FNA was performed and aspirated purulent material. The patient was hospitalized she presented afebrile but with leukocytosis with left deviation, with normal thyroid function. The cervical tomography presented an image suggestive of an abscess in the peritireoid region on the right side that connected with the esophagus. After stabilization, improvement of the symptoms and slight decrease of the cervical volume, she was evaluated by the surgical team, and opted for clinical treatment for scarring of the fistula first and evaluation the need for a surgical approach in a second moment after a new cervical tomography. **Discussion:** Suppurative thyroiditis is caused by an infection of the thyroid gland. The signs and symptoms may be similar to chronic thyroiditis and subacute granulomatous thyroiditis and other noninfectious inflammatory conditions. But for our patient the tomography excluded the previous hypothesis of thyroid abscess. Our patient had a cervical abscess due to a foreign body trapped during swallowing in the digestive tract. Foreign bodies trapped during swallowing are common. Digestive endoscopy is diagnosed in 94% of the cases and allows its removal. They generate perforations, abscesses or lesions of large vessels. **Final comments**: We report the case of a patient with an abrupt onset cervical volume with fever and local pain. The differential diagnosis is made with thyroiditis, but we are faced with normal laboratory tests and image examination demonstrating a lesion suggestive of peritireoid abscess secondary to esophageal fistula due to foreign body ingestion.

56594 CLINICAL AND LABORATORIAL EVALUATION OF PATIENTS WITH MULTINODULAR GOITER SUBMITTED TO TOTAL THYROIDECTOMY

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The term goiter is used to describe an increase in thyroid volume, which may be diffuse or in the presence of multiple nodules. Thyroid function is usually normal and may be associated with both hypo and hyperthyroidism. Goiter should be evaluated according to size and nodules characteristics, besides symptoms and signs of tracheal compression. In our service, surgical treatment is always indicated in the presence of retrosternal goiter, tracheal deviation, presence of nodule(s) > 4 cm and indeterminate thyroid cytology. **Objective:** To evaluate the clinical and laboratory characteristics of patients submitted to total thyroidectomy (TT) by goiter and thyroid status and calcium metabolism after 6 to 12 months. **Patients and methods:** Patients submitted to TT in Tertiary Hospital for goiter from 2011 to 2015, with follow-up for at least 6 months after surgery, were evaluated. Patients with Graves' disease, with Bethesda V and VI thyroid cytology or who had previous thyroid surgery or previous radioiodine therapy and associated hyperparathyroidism were excluded. **Results:** Out of 100 patients operated, 75 patients (66 F: 9M), with a mean age of 54.3 ± 12.6 years (27 to 78 years) were included. Previous hypothyroidism was present in 8% and only 4% had subclinical hyperthyroidism. Antithyroperoxidase and antithyroglobulin were present in 16% and 24%, respectively. Compressive symptoms were observed in the vast majority (70%), most being dyspnea. Retrosternal goiter was detected by tomography in 28% and tracheal deviation in 78%. Thyroid volume determined by ultrasonography ranged from 15 to 636 mL. Differentiated thyroid carcinoma was diagnosed in only 8 patients. Definitive hypoparathyroidism was established in 17%. After 6 months of TT, 16% had suppressed TSH and 37% TSH > 4 mIU/L. After 12 months, 20% had TSH suppressed and 41% TSH > 4 mIU/L. **Conclusions:** TT is the treatment of choice to goiter with trachea deviating and retrosternal goiter, but definitive hypoparathyroidism was frequent (17%) in our institution. It is noteworthy the high frequency of excess and also the lack of levothyroxine in long term, revealing the difficulty of adjusting hormonal treatment after TT.

55561 THE GOITER IN MODERNISM ARTWORKS BRAZILIAN – GOITER IN PAINTINGS BY DI CAVALCANTI

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Introduction: Goiters appear in art works of many cultures, represented mainly by paintings and drawings. Di Cavalcanti was a Brazilian painter who sought to produce a form of Brazilian art free of any noticeable European influences. Fascinated by the daily life of the Brazilian, Di Cavalcanti does not unnoticed the women of the society of his time, since very many representations are to be found within the works he produced. **Objective:** To list Di Cavalcanti artworks in which goiters are represented. **Method:** Was made observational evaluation of 130 paintings from the 20s and 70s of the last century (http://www.dicavalcanti.com.br/obras.htm). Evaluation was made of the neck and face (goiter, thick neck, and cretinism appearance). **Results:** When taking look at the women paintings of this Brazilian artworks painter, were identified 13 portrayed women demonstrating an abnormal profile of the neck with swelling, suggestive of a presumptive diagnosis of goiter, without evidence of cretinism appearance. Of the 13 paintings suggestive of goiter, 10 were painted between the 20s and 50s of the last century (period of iodine deficiency in Brazil), and 3 between the 60s and 70s of the last century. **Conclusion:** The life imitates "art", and the artist cited was not physician, and probably did not have intention to illustrate a pathological condition, though the observations of the images in this study should be considered as goiter or thick neck.

56667 USE OF METHIMAZOLE FOR RADIOIODINE THERAPY IN MULTINODULAR GOITER: A CASE REPORT

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Case presentation: A 65-year-old woman was complaining about cervical discomfort associated with dysphagia, but without clinical symptoms of thyrotoxicosis. Admitted for evaluation, her thyroid ultrasonography showed multinodular goiter with partially cystic nodules in the left lobe, and a thyroid volume of 133 mL. Despite having suppressed TSH (0.02 mcUI/mL) with normal free T4 (1.34 ng/dL), scintigraphy showed a normofunctional thyroid (18.9% RAIU at 24 hours) with a cold nodule present in the left lobe. Through fine needle aspiration, the investigation revealed the nodule as compatible with adenomatous goiter. Even with a bulky goiter and a compressive symptom, a radioiodine treatment was the choice due to a long surgery roster in the hospital. Thus, methimazole (40 mg/day) was used in order to increase endogenous TSH, thereby improving thyroid uptake of I-131. With a TSH of 7.12 mcUI/mL, the patient received a radioiodine dose of 50 mCi. After 6 months of radioiodine therapy, there was reduction of the thyroid volume (36,9 mL) with improvement of compressive symptoms. The patient had subclinical hypothyroidism, with no need for levothyroxine replacement. **Discussion:** Despite the high prevalence of multinodular goiter (MNG), the treatment is not a consensus. Surgery is still the first choice for patients with compressive symptoms. However, the use of radioiodine is increasing due to its safety, low cost, and possibility of ambulatory care. Although the use of recombinant TSH (rhTSH) in MNG has no recommendation, it has been largely used on clinical practices to increase I^{131} intake (RAIU) and to make it more homogeneous, with good results. Some authors have also reported the use of methimazole (MTZ) to increase endogenous TSH, with rise in RAIU, and thyroid volume reduction. There is also improvement of double the iodine uptake, reducing the required dose of radioiodine. Furthermore, there is evidence of higher risk of hypothyroidism. Even though the use of antithyroid drugs is known to reduce the effectiveness of radioiodine, there have been cases where the withdrawal of MTZ 7 days before the radioiodine dose have lead to positive results. **Final comments** Radioiodine may be the first choice for patients with MNG and compressive symptoms that cannot submit to surgery. However, a proper iodine intake is necessary for positive results. MTZ can be useful as an alternative to rhTSH use, enhancing radioiodine intake, and reducing thyroid volume with low cost.

NTI SYNDROME

56580 SEPSIS DECREASE THRA AND MITOCHONDRIAL CONTENT IN THE DIAPHRAGM

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Introduction: Besides the effort to manage sepsis, patients often die due major organ collapse, including respiratory failure. The diaphragm is the main respiratory muscle, and its dysfunction is a common cause to intensive care unit (ICU) hospitalization. Severe illnesses lead to the non-thyroid illness syndrome (NTIS), an unbalance in thyroid hormone (TH) signaling. TH is a major regulator of muscle and mitochondrial function. Recently, our group showed that acute sepsis induces change in the muscle fiber profile and reduction in local TH signaling. However, chronic inflammation had the opposite effects. Our previous data leads us to speculate if the differences observed are due to the duration or severity of the illness. **Objectives:** Investigate if TH signaling could be related to diaphragm impaired function in acute and chronicle septic patients due to the changes in mitochondrial function. **Methods:** Cecal ligation and puncture (CLP), most widely used model to study the etiology of human sepsis, were performed in 12 weeks-old C57Bl/6 male mice, control mice were sham operated. All animals received antibiotics (imipenem 25 mg/kg) 8h and every 24h after the surgery. The diaphragms were snapping frozen from acute (24h) or chronicle (120h) mice. We investigated the RNA expression by qPCR of: Dio2 (D2), Thra1, Vdac1 (mitochondrial DNA if correlated to genome reference gene: Phactr4), Ppargc1a, Opa1 and Dnm1l. The data were analyzed from at least 5 animals per group and are expressed as mean ± SEM. **Results:** We observed a decrease in Thra in the 24h septic group (1.5 ± 0.2 sham, 0.3 ± 0.1, $p < 0.05$) and no difference Dio2 expression in both groups. There was a decrease in Ppargc1a expression in acute (1.56 ± 0.42 sham, 0.15 ± 0.05 CLP, $p < 0.05$) and chronicle CLP (2.0 ± 0.5 sham, 0.8 ± 0.1 CLP, $p < 0.05$) groups, which could indicate decrease in mitochondrial biogenesis. The mitochondrial gene content seems to be decreased in both acute (10.6 ± 1.0 sham, 6.3 ± 1.1 CLP) and chronicle (14.6 ± 0.9 sham, 7.5 ± 0.7 CLP, $p < 0.05$) mice. We observed an increase in Dnm1l, a marker of mitochondrial fission in the chronic group (0.57 ± 0.04 sham, 0.93 ± 0.09 CLP, $p < 0.05$) and no difference in mitochondrial fusion marker Opa1. **Conclusion:** Our data suggest a decrease in mitochondrial content due to sepsis, which could be associated to a decreased action of TH in the diaphragm. Also, we suggest that a reduction in mitochondria function could lead to diaphragm failure in sepsis and NTIS patients.

THYROID AND METABOLISM

55867 ASSOCIATIONS BETWEEN LOW THYROID FUNCTION AND CARDIOVASCULAR RISK FACTORS IN ELDERLY PATIENTS WITH METABOLIC SYNDROME

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Introduction: Metabolic syndrome (MetS) is mostly associated with a proinflammatory state and displays an increasing prevalence with age. Recently, low thyroid function has been also linked to the increase of MetS prevalence. Indeed, it has been suggested that this relationship may be extended to patients with elevated TSH but within euthyroidism. **Objectives:** Our aim was to study the association of elevated TSH values with inflammatory and metabolic cardiovascular risk factors in elderly euthyroid MetS patients. **Methods:** Patients > 65 years with MetS that consulted or were referred to our Endocrine Unit were prospectively recruited. TSH and free T4 serum levels were determined together with several metabolic, proinflammatory and anthropometric parameters. Only those patients with euthyroidism (TSH: 0.3-6 mU/L and free T4: 0.7-1.8 ng/dL) were included. Non-parametric correlation tests and ANOVA were used for statistical analysis. **Results:** One hundred and fifty two patients (100 women/52 men) participated in the study. TSH levels were correlated with total cholesterol ($r = 0.20$, $p < 0.01$) and non-HDL-cholesterol ($r = 0.21$, $p < 0.01$). Nonetheless, as women showed different prevalence of cardiovascular risk factors and higher TSH levels than males (+30%, $p < 0.05$), the following analyses were performed in each gender separately. Spearman correlation between TSH and IL-6 was significant only in the female group ($r = 0.27$, $p < 0.05$), in whom there was a lower prevalence of smoking and diabetes than in men. In addition, when adjusting by diabetes and smoking, the correlation between TSH and IL-6 remained significant ($r = 0.27$, $p = 0.03$). In men, TSH correlated with HOMA ($r = 0.27$, $p < 0.05$), and non-HDL-c ($r = 0.27$, $p < 0.05$). **Conclusions:** Sex-specific associations were found between elevated TSH levels within the euthyroid range and proinflammatory and metabolic cardiovascular risk factors in elderly patients with MetS. In the female sex in particular, IL-6 was directly associated with increasing TSH levels while in men TSH values were related to insulin resistance and increased lipids.

56686 COMPARISON BETWEEN THE GUIDELINES OF THE AMERICAN AND EUROPEAN ASSOCIATIONS FOR THE TREATMENT OF SUBCLINICAL HYPERTHYROIDISM

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Introduction: There is an ongoing debate regarding the risks and benefits of treating subclinical hyperthyroidism (SCH), defined as low serum TSH levels in face of normal thyroid hormones concentrations. However, new guidelines have recently been published by the American (ATA) and European (ATA) Thyroid Associations. **Objectives:** To evaluate the main differences between ATA and ETA guidelines on subclinical hyperthyroidism in clinical practice. **Methods:** Retrospective analysis of a cohort of outpatients with endogenous SCH followed in our hospital from 2010 to 2016. SCH was defined as serum TSH levels < 0.45 mU/L in the presence of normal serum free T4 (FT4) and total T3 (T3), persistent for at least six months. Patients with previous history of thyroid disease, severe systemic disease or psychiatric illness, taking thyroid hormones, antithyroid drugs, amiodarone, lithium or glucocorticoids, and pregnant women were excluded from the sample. **Results:** 156 patients (83% female) with a mean age of 61.1 ± 14.5 years were included in this study. At baseline, the mean serum levels of TSH, FT4 and T3 were 0.13 ± 0.11 mU/L, 1.25 ± 0.21 ng/dL and 1.24 ± 0.27 ng/mL, respectively. SCH grade I (TSH 0.1-0.45 mU/L) occurred in 45% and SCH grade II (TSH < 0.1 mU/L) in 53% of the patients. The etiology of SCH was toxic multinodular goiter (73.1%), toxic adenoma (14.1%), and Graves' disease (12.18%). According to the criteria (of treating or considering to treat) by ATA (n = 133, 85.3%) and ETA (n = 131, 84%) guidelines, we would recommend the treatment for most of the patients (p = 0.86). The guidelines agreed to treat 92% of the patients. Among the patients in whom the guidelines disagreed, eight of them would have the treatment recommended only by the ATA criteria, while five of them only by the ETA criteria (p = 0.17). In general, treatment was recommended by both guidelines based on the level of TSH suppression (TSH < 0.1 mU/L), age (> 65 years), and on cardiovascular and other risk factors. However, there are still some divergences between them, such as the recommendation to treat postmenopausal women without hormonal replacement therapy or using bisphosphonate by ATA, and treatment, based on the SCH etiology by ETA. **Conclusions:** Despite few divergences between the studied guidelines, treatment was recommended for most patients with endogenous SCH by both ATA and ETA SCH guidelines.

55127 EVALUATION OF THYROID FUNCTION IN SUBJECTS WITH RECENTLY DIAGNOSED AND UNTREATED THYROID DISEASE

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Introduction: The determination of thyroid dysfunction is part of the clinical investigation in different medical specialties. Non-thyroid disorders, certain medications and age may affect the hormonal results. The presence of anti-TSH or anti-thyroid hormone antibodies may result in abnormal findings. **Objective:** To evaluate thyroid function parameters in a group of subjects with recently diagnosed and untreated thyroid disease taking no medication. **Cases:** The study was conducted on 301 patients of both sexes, 275 of them non-pregnant women (91.3%) aged 18 to 87 years and 26 of them men (8.7%) aged 21 to 85 years. The subjects were compared to 166 control patients with no thyroid disorders, 123 of them women (75.3%) aged 18 to 81 years and 43 of them men (24.7%) aged 19 to 66 years. The patients were divided into the following groups: Group A – Control Patients; Group B – Subclinical Hypothyroidism; Group C – Clinical Hypothyroidism; Group D – Subclinical Hyperthyroidism; Group E – Clinical Hyperthyroidism; Group F – Chronic Thyroiditis; Group G – Goiter; Group H – Papilliferous Carcinoma; Group I – Previous Hyperthyroidism. **Results:** The female sex was preponderant in all groups, with no males occurring in the Clinical Hyperthyroidism, Papilliferous Carcinoma or Previous Hyperthyroidism groups. Patients with Subclinical Hyperthyroidism and Goiter belonged to significantly older age ranges. Mean TSH values were higher in the Clinical and Subclinical Hyperthyroidism Groups. Free T4 and T3 levels were significantly lower in Clinical Hypothyroidism and significantly higher in Clinical Hyperthyroidism. Mean Thyroglobulin levels were significantly higher in the Goiter Group and mean Anti-Thyroglobulin antibody (Anti-Tg) and Anti-Thyroperoxidase (Anti-TPO) levels were significantly higher in the Chronic Thyroiditis group. The Anti-TSH receptor (TRAB) antibody was significantly higher in the Clinical Hyperthyroidism Group and the finding of Toxic Multinodular Goiter predominated in the Subclinical Hyperthyroidism Group. **Conclusion:** Autoimmune thyroid disorders predominated among females and in the less advanced age ranges and structural thyroid disorders and high thyroglobulin level predominated in the more advanced age ranges. Acknowledgment to the Endocrinology Leage of Unaerp years 2015 and 2016 and to Unaerp for the support.

56710 FRUCTOSE INTAKE INDUCES MOLECULAR ADAPTATION IN BROWN ADIPOSE TISSUE INVOLVING THYROID RELATED-GENES

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Introduction: Thyroid hormones (THs) are essential for the maintenance, development and homeostasis of the body. Therefore, changes in thyroid function are associated with changes in body weight, energy expenditure, insulin sensitivity and dyslipidemia. Fructose is a carbohydrate widely used in the industry, and the high consumption of fructose has been associated with metabolic disorders such as hyperglycemia, dyslipidemia, hepatic steatosis, hypertension and obesity. Despite the importance of THs for the metabolism regulation, the effects of fructose consumption on thyroid function have been poorly investigated. **Objectives:** Study the effects of fructose consumption on thyroid function. **Methods:** Male Wistar rats were divided into 2 groups (n = 8): Control (CT) and Fructose (FT). The FT group received the fructose diluted in drinking water (10%) for 3 weeks ad libitum (Ethics Committee #757/2016). Thyroid, liver, visceral adipose tissue (epididymal and retroperitoneal) and brown adipose tissue (BAT) were weighed and frozen for analysis. Blood glucose, serum triglyceride and cholesterol were analyzed by colorimetric assays. mRNA gene expression in brown adipose tissue was analyzed by qPCR. **Results:** The FT group showed a non-significant increase in visceral fat (P = 0.073), accompanied by an increase in glucose levels (P = 0.0099) compared to CT, indicating resistance to insulin effect. In addition, we observed an increase in liver (P = 0.017) and BAT weight (P = 0.0044) in FT, which could indicate an accumulation of fat in these tissues. Concern lipid profile, the fructose group showed an increase in serum triacylglycerol (P = 0.0150) with no change in cholesterol. These results showed that supplementation with fructose for 3 weeks caused metabolic disturbances. The fructose intake promoted higher thyroid weight and higher expression of TRα (P = 0.0009), TRβ (P = 0.0004) and D2 (P = 0.0002) mRNA in the BAT. Increased expression of D2 in BAT and thyroid hypertrophy may indicate thyroid dysfunction and lower serum concentration of THs. Fructose-treated animals also exhibit higher mRNA expression of UCP1 (P = 0.0023), SREBP1c (P = 0.003) and PPARα in BAT (P = 0.0118), suggesting stimulation of thermogenesis, lipid synthesis and oxidation in this tissue. **Conclusion:** The consumption of fructose for 3 weeks induced changes in BAT gene expression, suggesting increased activity of this tissue. In addition, fructose intake might induce thyroid dysfunction that will be further investigated

56687 INCREASED PREVALENCE OF CHRONIC KIDNEY DISEASE IN SUBCLINICAL HYPOTHYROIDISM – THE JAPANESE-BRAZILIAN THYROID STUDY

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Introduction: Thyroid hormones have an important effect on the renal function, and it is well known that overt hypothyroidism is associated with low estimated glomerular filtration rate (eGFR) and with an increased prevalence of chronic kidney disease (CKD). However, the impact of subclinical thyroid disease on the renal function remains uncertain. **Objectives:** To investigate the effects of subclinical thyroid disease on renal function in population-based study. **Methods:** In a cross-sectional analysis, an overall of 1,110 Japanese-Brazilians aged above 30 years old, free of thyroid disease, and not taking thyroid medication at baseline were studied. eGFR was calculated using the Modification Diet in Renal Disease (MDRD) equation. Odds Ratio (OR) [95% confidence interval (CI)] was estimated for the prevalence of mild CKD (eGFR 60-89 ml/min per 1.73 m^2), moderate CKD (eGFR 45-59 ml/min per 1.73 m^2) and severe CKD (eGFR < 45 ml/min per 1.73 m2). **Results:** A total of 913 (82.3%) participants had euthyroidism, 99 (8.7%) had subclinical hypothyroidism (SChypo), and 69 (6.2%) had subclinical hyperthyroidism (SChyper). Compared to individuals with euthyroidism (119,2 ml/min/1.73 m^2), the eGFR was significantly higher in individuals with SChyper (132,9 ml/min/1.73 m^2; p = 0,04) and decreased, but not statistically different, in those with SChypo (118,0 ml/min/1.73 m^2; p = 0,9). The prevalence of severe CKD [OR = 6,01 (95% CI: 1,9-19,4)] was higher in individuals with SChypo compared to those in euthyroidism, but no differences were found in the prevalence of moderate [OR = 1,58 (95% CI: 0,68-3,89)] or mild CKD [OR = 1,37 (95% CI: 0,84-2,23)]. In a subsequent subanalysis, the increased prevalence of severe CKD persisted only in the < 65 year age group with SChypo compared to euthyroidism. **Conclusion:** Compared to euthyroidism, individuals with SChyper had an increased eGFR, and younger participants < 65 years with SChypo had a higher prevalence of severe CKD. However, our cross-sectional study design does not allow us to establish whether these alterations are cause or consequence of CKD.

56708 THYROID FUNCTION EVALUATION IN BARIATRIC SURGERY POSTOPERATIVE PATIENTS

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Introduction: Insulin and leptin resistance presents in obesity seems to mediate TRH hypothalamic regulation in obesity patients. A raise in serum thyroid stimulating hormone (TSH) can be observed in obesity patients especially in class 2 and 3 individuals. Treating subclinical hypothyroidism in obese seems not be effective for improve weight loss in those patients. **Objectives:** We evaluated thyroid function in obese patients pre and 6 months after bariatric surgery. **Methods:** Serum levels of TSH and free thyroxin (FT4) of 52 patients submitted to bariatric surgery were analyzed pre and 6 months after surgery. Mean differences were analyzed using T-test. TSH values 6 months after surgery were correlated with weight loss excess; we used Pearson test for correlations. All data were analyzed used IBM SPSS statistic 22. **Results:** Patients mean age were 44.7 years (± 9.6); 47 were woman (90.4%) and 5 men (9.6%); pre-operative body mass index were 47 kg/m² (± 7.3). Mean weight pre and 6 months post-operative were respective 123.3 kg (± 22.9) and 90.4 kg (± 18.4). Pre-operative TSH and FT4 means were respective 2.05 mUI/L (± 1.0), and 1.0 ng/dL (± 0.7), post-operative mean values of TSH and FT4 were respective 1.7 mUI/L (± 0.8) and 1.0 ng/dL (± 0.3). There were a significant difference between pre and 6 months post-operative TSH means (p = 0.03). Weight loss excess and TSH were negative correlative 6 months after surgery (r = -0.33; p = 0.001). **Conclusions:** Weight loss may contribute for falls in TSH levels after bariatric surgery and it seems to be proportional to excess weight loss.

56691 HIGH PREVALENCE OF UNSUSPECTED CONGENITAL HYPOTHYROIDISM USING A LOW TSH CUTOFF VALUE FOR NEONATAL SCREENING

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Introduction: In 2015 the guidelines of the Brazilian Neonatal Screening Program (BNSP) advocated the use of a neonatal TSH (TSHneo) cutoff value of 10 mU/l for newborn screening of congenital hypothyroidism (CH). However, there is a trend around the world of lowering the TSHneo cutoff value in order to increase the sensitivity of the assay to detect children with unsuspected CH. **Objectives:** To assess the impact of lowering the TSHneo cutoff value from 10 mU/l to 5 mU/l for the screening of CH in the region of Marilia, State of São Paulo, Brazil. **Methods:** Data were retrospectively collected from the clinical records of all children with TSHneo ≥ 5 mU/l at the newborn screening followed in our hospital from January 2012 to February 2017. Results were virtually compared with those advocated by the BNSP (10 mU/l), interesting the rates of false-positive diagnosis, permanent CH, and thyroid dysgenesis. Thyroid ultrasound was performed in 70 (51.8%) children at 2 years of age, and a clinical reassessment was performed in 52 (38.5%) children at 3 years of age after levothyroxine withdrawal. **Results:** The children included were divided into two groups: Group I (G1), TSHneo 5-9.9 mU/l (n = 99, 73.3%) and Group 2 (G2), TSHneo ≥ 10 mU/l (n = 36, 26.6%). The mean TSHneo was 6.5 mU/l (5.0-9.8) and 71.5 mU/l (10-309 mU/l) in G1 and G2, respectively. As expected, the rates of false-positive diagnosis were significantly higher in G1 than in G2 (37.7% *vs.* 9.1% p = 0.002), but a clinical re-evaluation at 3 years of age showed a similar rate of permanent CH in both studied groups (G1, 85.2% *vs.* G2, 96.0%; p = 0.18). The frequency of thyroid dysgenesis was higher (p = 0.0003) in G2 (n = 15, 51.7%), but surprisingly, it was not negligible in G1 (n = 5, 12.2 %). **Conclusion:** In this study, lowering the TSHneo cutoff value to 5 mU/l allowed the detection of 23/135 children (17%) with permanent CH, including 5 with thyroid dysgenesis that would have been missed using the 10 mU/l cutoff.

THYROID AND PEDIATRIC DISEASE

56103 PRESENTATION AND EVOLUTION OF GRAVES' ORBITOPATHY IN CHILDREN

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Introduction: Graves' disease (GD) is rare in pediatric population, and the main cause of hyperthyroidism. However, there are few studies regarding Graves' ophthalmopathy (GO) and the outcomes in childhood and adolescence patients. **Objective:** Evaluate the frequency, characteristics and evolution of the GO at a single university center. **Methods:** We study 885 GD patients from 1995 to 2016, and 19 (2.1%) patients) were under 18 years. These patients were classified according to sex, ethnicity, thyroid function, presence of anti-TPO and TRAb antibodies, evaluation of GO by Clinical Activity Score (CAS) and clinical evolution. Furthermore, they were divided in two groups according to presence of GO. **Results:** Most of the patients (63%) were female, 71% were Caucasian and the average age at presentation was 13 ± 3 (SD) years. Only 16% had a family history of GD, TRAb and anti TPO were positive in 89% and 74% respectively. Serum TSH was 0.12 ± 0.41 IU/L and free T4 5.08 ± 3.79 ng /dL at diagnosis. GO was observed in six patients with the following distribution: CAS 4 = 1 patient, CAS 3 = 1 patient, CAS 2 = 2 patients and CAS 1 = 2 patients. The proptosis were 12 ± 3 mm (normal value = 14.2 ± 1.8 mm) and the eyelid 16 ± 3 mm (normal value = 2.5-5 mm). No differences were observed between patients with GD who had a family history of the disease from those without familiar history of GD ($p < 0.05$). There were no differences between the groups regarding the variables mentioned. The treatment with methimazole in titration regimen was used for a period of 14 to 36 months. At the end of the treatment all patients returned to euthyroidism and an excellent evolution of CAS was noted returning to zero in all patients. **Conclusion:** Children and adolescents rarely present GO however, if is present, most cases are mild to moderate. GO remission can be obtained with long term treatment with methimazole.

THYROID AND PREGNANCY

56673 ACUTE EXPOSURE TO LIPOPOLYSACCHARIDE (LPS) MODIFIES THE EXPRESSION OF PLACENTAL DEIODINASES AND THYROID HORMONES TRANSPORTERS

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Introduction: Thyroid hormones (TH) are critical for fetal growth and exhibit utmost important actions mediating proper developing and maturation of the mammalian brain. Maternal TH supply is particularly important at early stages of pregnancy, but as gestation proceeds, the fetus starts its own production, becoming less dependent on maternal levels. In this context, placental deiodinase and TH transporters allow the transfer of adequate TH levels to the fetus. Lipopolysaccharide (LPS), classically used to model of nonthyroidal illness syndrome, can regulate deiodinases and TH transporters in a variety of organs such as muscle, liver and lung, however, little is known about its effects regulating placental TH transfer in different gestational stages. Therefore, we hypothesized that pregnant dams exposed to LPS, a toll-like receptor (TLR)-4-agonist, exhibit a distinct pattern of deiodinases and TH transporters expression in the placenta. **Methods:** Pregnant female mice (C57BL/6, 8-10 weeks) were exposed to LPS (150 µg/kg-ip) or vehicle (PBS) at the following embryonic (E) stages: E15.5 (mid-gestation: n = 8/group) and E18.5 (late pregnancy: n = 9-10/group). Animals were sacrificed 4h after challenge and placentas were collected. qPCR was used to analyze the expression of important placental TH-metabolic genes, such as: the TH transporters, Slc16a10 (Mct10), Slc7a5 (Lat1), Slco1c1 (Oatp1c1), and the TH activation (Dio2) or inactivation (Dio3) deiodinases enzymes. **Results:** No significant differences were observed at the fetal to placental weight ratio after LPS exposure on both time-points. A gestational-age dependent placental expression of Slc16a10 (Mct10), Dio2 (D2), Slc7a5 (Lat1) and Slco1c1 (Oatp1c1) was observed. At E15.5 stage, placental expression of Slc16a10 (Mct10), Dio2 (D2), Slc7a5 (Lat1) was significantly decreased ($p < 0.05$), whereas only placental Slco1c1 (Oatp1c1) expression was elevated at E18.5 stage. **Conclusions:** LPS (bacterial) exposure during mid- and late-pregnancy has the potential to impact placental TH metabolism. Our data suggest that placental TH metabolism is more abundantly affected at earlier stages, when the fetus is highly dependent upon maternal supply of TH. The impact of these changes to fetal development clearly requires more investigations. **Funding:** Bill and Melinda Gates Foundation, CNPq, Faperj and Capes.

56620 AVALIAÇÃO DA SUFICIÊNCIA IÓDICA DURANTE OS TRÊS TRIMESTRES DE GESTAÇÃO

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A gestante apresenta maior necessidade de iodo para suprir a maior produção de hormônios tireoidianos. Como o estado de São Paulo é considerado uma região suficiente em iodo, de acordo com a OMS, a suplementação iódica rotineira não é recomendada. A deficiência de iodo causa elevação de TSH e consequentemente leva ao aumento do volume tireoidiano, compensando a produção dos hormônios tireoidianos. **Objetivo:** Correlacionar a suficiência de iodo e a função tireoidiana em gestantes, assim como o volume tireoidiano e a tireoglobulina sérica (TG). **Material e métodos:** Avaliamos gestantes de baixo risco, a cada trimestre de gestação, acima de 18 anos. Foram excluídas gestantes com doença tireoidiana prévia, com anticorpos antitireoidianos positivos e em uso de suplementos contendo iodo. A concentração de iodo urinário foi feita em amostra isolada pelo método Sandell-Kolthoff. As dosagens de TSH, T4, T3, T4 livre (T4L), T3 livre (T3L) e tireoglobulina (TG) foram feitas pelo método eletroquimioluminescente. Ultrassonografia da tireoide foi realizada com aparelho Philips IU-22 e transdutor 7,5-12 mHz. **Resultados:** Avaliamos 251 pacientes. As dosagens de iodúria não apresentaram diferenças estatísticas entre os três trimestres da gestação. As medianas foram de 133 µg/L, 147 µg/L e 157 µg/L, respectivamente. Encontramos deficiência de iodo (iodúria < 150 µg/L) em 52,2% das gestantes. Somente 4,4% apresentavam excesso de iodo (> 250 µg/L) Comparando o grupo com deficiência de iodo e o grupo suficiente em iodo (iodúria 150-250 µg/L), observou-se diferença significativa nos valores de TSH (TSH = 2,24 µIU/mL e 1,78 µIU/mL, p = 0,041) e de T3 (T3 = 196 ng/dL e 181 ng/dL, p = 0,024) nas gestantes do segundo trimestre. TG sérica e volume tireoidiano, assim como T4 e T4L, não apresentaram diferenças significativas entre os grupos. **Conclusão:** Encontramos deficiência iódica em 52,2% das gestantes avaliadas. Embora a deficiência de iodo encontrada tenha sido leve, identificamos TSH mais alto, assim como concentrações mais altas de T3 nesse grupo deficiente. Especulamos que exista uma produção preferencial de T3 à custa de elevação de TSH como possível mecanismo adaptativo nas gestantes com deficiência de iodo. Sendo assim, reforçamos que, apesar de essa região estudada ser suficiente em iodo, a suplementação iódica poderia ser recomendada, com cautela, para gestantes e lactantes, devido à alta prevalência de deficiência encontrada.

56619 HIGH RISK PREGNANCY IS ASSOCIATED WITH IODINE DEFICIENCY: A CROSS-SECTIONAL STUDY IN BRAZIL

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Introduction: High risk PW (HRPW) represents 10%-20% of all pregnancies and 50% of perinatal mortality. During pregnancy, the demand for iodine increases and, consequently, an estimated rise in daily iodine requirement of 50%-70% occurs, being around 250 µg/day. **Objective:** To analyze the iodine nutritional status, socioeconomic, demographic and anthropometric characteristics among HRPW screened at the main referral public health center at Bahia, Brazil. **Methods:** Cross-sectional study conducted in 241 HRPW (15-46 years-old) in Salvador, Bahia, Brazil. Urinary iodine concentration (UIC), socio-demographic data, anthropometric evaluation and neonatal TSH in filter-paper blood were performed. **Results:** The mean UIC (MUIC) was 140.6 ± 104 µg/L, median was 119 µg/L (25-75th, 58.7-200.4 µg/L), indicating mild ID. Low UIC (< 150 µg/L) was detected in 61.8% (N = 149) (18.3% between 100-150 µg/L; 24.5% between 50-100 µg/L and 19.1% with UIC < 50 µg/L. Indeed, none HRPW had UIC > 500 µg/L, indicating absence of excessive iodine intake (EII). Overall, 53,1% (N = 128) of HRPW was under low salt diet and 32,5% (N = 77) had hypertension. Among hypertensive women, 77,9% were under salt restricted diet (SRD) and a 112% increased risk of ID was observed [OR = 2,127 (1,178-3,829); p = 0.011]. SRD was associated with ID [OR = 1,82; IC: (1,073-3,088), p = 0,026]. **Conclusion:** A high prevalence of ID among HRPW was observed and hypertension or salt restriction were associated with increased risk of poor iodine intake. The lack of an apparent benefit of sodium restriction together with potential susceptibility for thyroid hormone abnormalities and worse obstetric outcomes reinforces that the practice of prescribing a low-salt diet to hypertensive PW should be abandoned. This study was supported by State of Bahia Research Foundation (Fapesb Edital 029/2012) grant (TOU PET0002/2013).

56578 MURINE MALARIA INFECTION MODIFIES THE EXPRESSION OF PLACENTAL THYROID HORMONE TRANSPORTERS AND DEIODINASES

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Introduction: Gestational malaria promotes inflammatory responses at the maternal-fetal interface, leading to reduced fetal viability, PTL and also the impairment of the HPT axis in a similar manner to which is observed in non-thyroidal illness syndrome (NTIS). Reduced maternal serum TH levels and uterine hypothyroxinemia are associated with intrauterine growth restriction (IUGR) and abnormal fetal-placental unit development. However, the effects of gestational malaria on the expression of placental TH transporters and deiodinases remain underexplored, as well as their relationship with PTL pathogenesis. **Objectives:** Evaluate the expression of placental TH transporters and deiodinases in a PTL model of Plasmodium Berghei ANKA infection. **Methods:** Female C57/BL6 mice (8-10 weeks of age) were mated. On gestational day E13.5 mice were infected intraperitoneally with Plasmodium Berghei ANKA (5x10^5 infected-erythrocytes, n = 13-16) or injected with PBS (n = 12) and sacrificed on E18.5. Maternal blood were collected to evaluate the parasitemia. Placental disks and maternal liver were collected and qPCR was performed to evaluate the expression of the following genes: Slc16a10 (MCT10), Slc7a5 (LAT1), Slc7a8 (LAT2), Slco1c1 (OATP1C1), Dio2 (D2) and Dio3 (D3) in the placenta; Dio1 (D1) and Il1b (IL1-β) in the maternal liver. **Results:** Mice infected with Plasmodium Berghei ANKA showed an average parasitemia of 16% infected-erythrocytes and an increase in spleen weight (153.8 ± 10.4 mg, $P < 0.001$) compared to control group (79.8 ± 3.4 mg). Malaria infection induced PTL in 20% of the infected pregnants. Fetal weight (843.9 ± 55.8 mg, $P < 0.01$) was reduced in malaria group, compared to control (1123 ± 47.5 mg). Furthermore, it was observed a reduction in Slc16a10 ($P < 0.01$), Slc7a5 ($P < 0.05$), Slc7a8 ($P < 0.05$), Dio2 ($P < 0.05$) and Dio3 ($P < 0.05$) mRNA expressions in the placenta of infected mice, a reduction in Dio1 ($P < 0.01$) and an increase in Il1b ($P < 0.01$) mRNA expression in the maternal liver. **Conclusion:** In the present study, we established a PTL model induced by malaria infection associated with a hallmark of NTIS in maternal liver and changes in the expression of TH transporters and deiodinases at the maternal-fetal interface. We speculate that this results in reduced TH/aminoacid transport from mother to fetus, leading to IUGR among surviving fetuses. We also hypothesize that these changes may lead to other consequences in fetal development, such as impairment of neural development.

56682 PRELIMINARY RESULTS OF THYROID ANTI-PEROXIDASE EVOLUTION IN PREGNANTS WITH PRIMARY HYPOTHYROIDISM AND LEVOTHYROXINE DOSE USED TO MAINTAIN NORMAL TSH

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Thyroid auto-antibodies are detected in more than 80% pregnant with hypothyroidism. Immune tolerance in pregnancy is an adaptive phenomenon that involves all aspects of the immune response and some studies found a decline in TPOAb and TGAb levels during pregnancy. **Objectives:** To evaluate the evolution of TPOAb during pregnancy and to observe if the decrease is related to the dose of levothyroxine used to treat primary hypothyroidism comparing with those TPOAb negative. **Methods:** 18 pregnant women with primary hypothyroidism were attended from 9.7 (6-15) weeks until the end of pregnancy and they started from normal TSH levels prior to gestation. All had TSH measured monthly and TPOAb before 24 weeks and in the third trimester [34.4 weeks (30-38)]. Eight had negative antibodies and ten had positive antibodies. It was compared LT4 dose used to obtain euthyroidism between the negative and positive antibody groups. In the group of positive antibodies was observed if the fall of TPOAb maintained relation with the LT4 dose used to maintain normal TSH. **Results:** In the group of negative antibodies LT4 dose in the beginning of pregnancy was 91.0 mcg/day and 1.8 ± 0.5 mcg/kg. At the end of pregnancy LT4 dose necessary to maintain normal levels of TSH was not different the beginning (105 ± 20.6 and 1.9 mcg/kg). Patients with positive TPOAb were divided into groups according to the evolution of TPOAb. Group 1: three patients in which TPOAb was unchanged throughout pregnancy (649.3 ± 513.6 *versus* 651.7 ± 510.8 IU/mL – NS); Group 2: six patients whose TPOAb decreased during gestation (397.8 ± 318.3 *versus* 116.8 ± 99 IU/mL – $p < 0.0001$). In one patient TPOAb increased (308.2 *versus* 1088). The level of TPOAb was significantly different between group 1 and group 2 ($p < 0.001$). In group 1 the patients had a need to increase the LT4 dose (increase 100% a day or 123%/kg). In group 2 there was a need to increase LT4 in 50% (3/6) of patients but, less than the previous group (increase of 64,1% a day/11,8%/kg – $p < 0,05$). In both groups LT4 dose were higher than in TPOAb negative patients. **Discussion:** In most patients TPOAb decreased during pregnancy. LT4 dose necessary for maintain normal TSH were higher in TPOAb positive patients. Lower TPOAb levels in the beginning of pregnancy that decreases until the end of this period could be related to need lower doses of LT4. This study is being expanded to better understand the relationship between TPOAb levels and LT4 dose during pregnancy.

56633 SUCCESSFUL PRENATAL TREATMENT OF FETAL HYPERTHYROIDISM

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Case presentation: We report a 26-years-old pregnant Chinese woman who speaks neither Spanish nor English. She had had a subtotal thyroidectomy for Graves' disease at age 19. On admission, she was at 19,6 weeks gestational age (wGA): FT4 1,26 (RR 0,7-1,7 ng/dL), TSH 0,02 (RR 0,5-3 mIU/L), TRAb 70 (NV < 15%). A fetal scan performed at 24,6 wGA showed fetal goiter (thyroid perimeter > 95 percentile). Another signs of fetal hyperthyroidism were absent. Fetal heart rate (FHR) was 150 beats/. Following initial fetal assessment, Selenium 200 mcg/d was indicated to the mother as an attempt to decrease TRAb levels. At 28 wGA, the presence of distal femoral ossification nucleus was noticed. Fetal hyperthyroidism was suspected and maternal treatment with Methimazole (MMI) 15 mg/d orally was started. Due to a gradual decrease in maternal FT4 levels (to 0,85 ng/dL), LT4 was added at 31,3 wGA to prevent maternal hypothyroidism. During MMI treatment, fetal thyroid perimeter diminished and it normalized by 34 wGA when maternal TRAb levels were 50%. FHR fluctuated from 150 to 120 beats/. MMI dose was progressively reduced from 15 mg/d to 2,5 mg twice a week at delivery. At 38 wGA a spontaneous vaginal delivery occurred, maternal FT4: 0,76 ng/dL and TSH: 0,56 mIU/L. Newborn: female sex, weight 2,840 kg, APGAR 9/10. Cord blood: FT4 1,43 ng/dL TSH 2,56 mIU/L TRAb 61%. At 11th postnatal day: FT4: 2,47 ng/dL TSH 0,05 mIU/L TRAb 53%. The newborn presented an adequate weight progress and her heart rate was always normal. At 67th postnatal day, TRAb levels were nearly normal (16%) FT4 1,48 ng/dL and TSH 2,78 mIU/L. **Discussion:** In mothers with active or in remission Graves' disease, fetal hyperthyroidism is suspected when maternal TRAb levels remains > 3 times the upper normal value since 20 wGA. Its prompt diagnosis allows an immediate treatment avoiding severe complications that may culminate with fetal death. **Final comment:** MMI+LT4 are an exceptional treatment during pregnancy. Following diagnosis of fetal hyperthyroidism (goiter + advanced bone age), we indicated MMI to the mother, only for fetal treatment and LT4 to prevent maternal hypothyroidism. The newborn was euthyroid at birth, which highlights the successful intrauterine treatment. Due to placental passage of high TRAb levels, there was a slight transient neonatal hyperthyroidism that resolved spontaneously when serum TRAb decreased. We emphasize the multidisciplinary work that allowed an adequate diagnosis and treatment.

56643 VITAMIN D STATUS AND THYROID AUTOIMMUNITY IN BRAZILIAN FIRST-TRIMESTER PREGNANT WOMEN

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Introduction: Maternal thyroid dysfunction and low ViD has been associated with pregnancy complications and adverse perinatal outcomes. However, few studies have evaluated the relationship between 25-hydroxy vitamin D (ViD) insufficiency and autoimmune thyroid diseases and showed conflicting results. In Brazil, there is sparse data on ViD status and thyroid-specific autoimmunity in pregnant women (PW) population. **Objective:** We prospectively evaluated the ViD status according to thyroid-specific autoimmunity and serum TSH levels in first-trimester PW. **Methods:** We included first-trimester PW who visited the prenatal care unit in Santo Antônio de Jesus/Bahia, between August/2013 and December/2014. After exclusion for lack of data, the study population comprised 102 first-trimester PW. The levels of thyrotropin (TSH), thyroid peroxidase antibody (TPOAb) and ViD were measured by chemiluminescence immunoassays. ViD insufficiency and deficiency were defined as serum levels lower than 20 and 30 ng/mL, respectively. Neonatal birth weight was registered. **Results:** The median age was 27 ± 6 (range 18-43) years. The median gestational age was 9.0 ± 2.2 weeks. The median level of TSH and ViD were 1.3 mUI/L (range 0.01-5.27) and 47 ng/mL (range 10.5-117.3), respectively. The overall prevalence of ViD deficiency, insufficiency and TPOAb positivity were 5.9%, 25.3% and 10.1%, respectively. The prevalence of TPOAb positivity in PW with TSH ≥ 2.5 mIU/L was 15.4%. The mean ViD levels were not significantly different between TPO Ab (+) and (-) PW (50 ng/mL *vs.* 51.6 ng/mL). The prevalence of ViD insufficiency/deficiency was not different between TPO Ab (+) and (-) PW (30% *versus* 24%, p = 0.33) but diverged between PW with TSH levels < 2.5 mIU/L *vs.* ≥ 2.5 mIU/L (23.3% *vs.* 38.5%, respectively) (p = 0.03). No correlation between ViD and the TSH levels was found (p = 0.48) but a negative correlation was found with TPO Ab levels (p < 0.0001). Birth weight did not changed between subgroups. **Conclusions:** Considering that our study population comprised healthy PW, the ViD insufficiency/deficiency prevalence was higher than expected. A significant higher prevalence of ViD insufficiency/deficiency was found among first-trimester PW with TSH levels greater than 2.5 mIU/L. Our study did not show a significant association between ViD insufficiency and thyroid autoimmunity in first trimester PW. **Support:** Fapesb.

THYROID AUTOIMMUNITY

56669 A CASE REPORT OF RIEDEL'S THYROIDITIS PRESENTING AS A CERVICAL MASS

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Case presentation: A 16-year-old female patient was referred to the Endocrinology Division due to a recent growth of a mass in the cervical region involving the right lobe (RL) of the thyroid with 3 months of progress. She presented a neck tightness sensation and dyspnea on heavy exertion. On examination, she had a mass in the RL of the thyroid with 6 cm of extension and it exceeded the midline. Neck and chest computed tomography (CT) revealed an expansive homogeneous lesion extending from the anterior mediastinum to the cervical visceral space measuring 9.9 x 4.2 x 3.8 cm. Laboratory tests were normal except for acute phase proteins. Pathologic and immunohistochemical study of the biopsied tissue showed chronic inflammatory process associated with extensive collagen fibrosis, involving soft tissue and thyroid, suggesting Riedel's thyroiditis (RT). Malignancy was ruled out. There was not a significant component of positive IgG4 cells. The patient received prednisone 60 mg, which was gradually reduced, and azathioprine 50 mg after 1 year. After 16 months of treatment, the patient is asymptomatic and the control image shows a reduction of the mass proportions. **Discussion:** RT is a rare form of chronic thyroiditis of unclear etiology characterized by extensive fibrosis involving the thyroid gland and its surrounding tissues. It has an estimated incidence of 1.06 cases per 100.000 outpatients and is more common in women. RT usually presents as a firm mass in the neck with compressive symptoms: dyspnea, like our patient, dysphagia, vocal cord paralysis, and jugular thrombosis. Most cases are clinically euthyroid at presentation, but 30%-40% develop hypothyroidism because of progressively gland infiltration. Differential diagnosis includes anaplastic thyroid cancer and lymphoma. Image exams will only suspect RT since its diagnosis remains based on surgical biopsy. Treatment includes corticosteroids, immunosuppression, and tamoxifen. Surgery may be indicated to relieve tracheal or esophageal compression, but extensive resection is not recommended because of the lack of resection planes and risk of injury to adjacent adhering structure. **Final comments**: RT is a rare disease and it should be considered in patients with fibrosis on the neck with normal thyroid function or hypothyroidism at presentation. The case described above had its diagnosis based on findings of examination, imaging and it was confirmed by biopsy, which is the gold standard method for diagnosis.

55868 ANTI-THYROID PEROXIDASE AND ANTI-THYROGLOBULIN ANTIBODIES POSITIVITY IN PATIENTS WITH HYPOTHYROIDISM - IS IT NECESSARY TO ASK FOR BOTH ANTIBODIES IN THE EVALUATION OF AUTOIMMUNE THYROID DISEASE?

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Introduction: Thyroid is a common target for autoimmune diseases (AID). Thyroid peroxidase antibodies (TPOAb) have been involved in the tissue destructive processes associated with the hypothyroidism observed in Hashimoto's and atrophic thyroiditis. There is some debate over the clinical utility of serum thyroglobulin antibodies (TgAb) measurements, since they do not appear to be a useful diagnostic test for AITD In areas of iodide sufficiency. The isolated positivity of TgAb showed no association with hypothyroidism or TSH elevations. **Objective:** To evaluate the prevalence of TPO and Tg antibodies positivity in patients with TSH levels higher than 10 mIU/L. **Methods:** We analyzed samples of both genders ≥ 12 years from a large database of a private reference clinical laboratory, tested for TSH, TPOAb and TgAb (ECLIA, Modular, Roche) in the period from January 2015 to December 2016. All the patients had TSH levels higher than 10 mIU/L. TPOAb and TgAb values, respectively, above 34 U/mL and 115 U/mL were considered positive. **Results:** 771 patients were evaluated, 72% women, mean age 52 ± 20 years; 316 (41%) of the patients had both negative antibodies; 455 (59%) presented positive TPOAb and/or TgAb. Analyzing these 455 patients, we found that 262 (58%) showed positivity of both antibodies; 147 (32%) only positive TPOAb and 46 (10%) only positive TgAb. 409 (90%) presented positive TPOAb regardless of TgAb levels (positive or negative) and 308 (68%) presented positive TgAb regardless of TPOAb levels. **Conclusions:** We found a higher positivity of TPOAb comparing with TgAb in patients with hypothyroidism, TSH higher than 10 mIU/L. Most of the patients that were TgAb positive were also TPOAb positive. Measurement of TPOAb only, allowed the diagnosis of thyroid autoimmunity in 90% of patients, suggesting that concomitant measurement of TPOAb and TgAb may be dispensable in routine evaluation of thyroid autoimmunity.

55560 DE QUERVAIN THYROIDITIS – CONVENTIONAL B-MODE ULTRASOUND AND COLOR DOPPLER IMAGING ASPECTS

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Introduction: De Quervain thyroiditis or subacute granulomatous thyroiditis is a self-limiting subacute inflammatory disease of the thyroid and constitutes nearly 3%-6% of all thyroid diseases, that occur typically following a viral illness. **Objective:** The present iconographic essay presents the main conventional B-mode ultrasound and color Doppler imaging aspects of De Quervain thyroiditis or subacute granulomatous thyroiditis. **Method:** The authors illustrate the present pictorial essay about De Quervain thyroiditis with conventional B-mode ultrasound and color Doppler images obtained in our institution over the past years. The main sonographic findings are discussed. **Conclusion:** De Quervain thyroiditis is a relatively uncommon disease, but ultrasound and color Doppler findings may suggest the diagnosis.

56631 ECHOGRAPHIC PATTERNS IN ANTITHYROID PEROXIDASE ANTIBODIES POSITIVE PATIENTS

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Antithyroid peroxidase antibodies (TPOAbs) are early markers of autoimmune thyroid disease (ATD). Although they are present in 90% of chronic thyroiditis (CT), they can also be found in 10% of population without apparent thyroid disease. Ultrasound can provide useful features related to high inflammatory activity. **Objectives:** 1) Describe ultrasound characteristics (USc) in patients with positive TPOAbs; 2) Compare echographic patterns (EP) with time since CT diagnosis (TDX), thyroid volume (TV), TPOAbs, levothyroxine treatment (LT4) and TSH levels; 3) Determine isthmus thickness (IT) and compare it with a control group without CT. **Methods:** Prospective study: 102 consecutive patients with positive TPOAbs were included from 2016 to 2017. Median TPOAbs was 600 IU/mL (R: 45->1000). Control group: 50 patients TPOAbs negative with nodular goiter. US was performed by the same operator with the same equipment, evaluating TV (by ellipsoid formula), USc and nodularity. EP (adapted from Ormeci 2016) were classified as: EP1: homogenous, EP2: indeterminate, EP3: established thyroiditis, EP4: atrophic thyroiditis. TSH and TPOAbs were measured by chemiluminescence IMMULITE (RV: TSH: 0.4-4.0 mIU/L, TPOAbs < 20 IU/ml). **Results:** Median age was 49 years (R: 17-79), 96.1% were females. Median TDX was 24 months (R: 0-300). 73.5% were under LT4. Median TSH 3.02 (R: 0.03-20). EP1, EP2, EP3 and EP4 were present in 10%, 28.4%, 42.2% and 19.6% of the patients, respectively. Of the USc, severe fibrosis was associated with TPOAbs > 1000 in 80% of the cases ($p = 0.003$). Nodules were present in 53% cases. Comparison between all EP showed the following: A) TPOAbs were higher in EP3 (756) ($p = 0.001$); B) TSH was higher in EP3 (9.3) ($p = 0.008$); C) TV was higher in EP3 (20.52) and lower in EP4 (5.1) ($p = 0.000$). 70% and 90% of patients with EP3 and EP4 received LT4, respectively, *versus* 30% with EP1 ($p = 0.006$). Mean IT was 4 mm *versus* 2.7 mm in control group ($p = 0.006$). **Conclusions:** 10% of patients with positive TPOAbs showed EP1; this could be the initial stage of CT and whose evolution is uncertain. Severe fibrosis was associated with TPOAbs levels >1000. EP3 showed higher TV, TSH and TPOAbs levels, and EP4 was associated with greater TDX and lower TV. The isthmus thickness was larger in TPOAbs positive cases than in the control group, as an indicator of diffuse thyroid involvement.

56590 EVALUATION OF THE TRAB AND ANTI-TPO AS PREDICTORS OF TREATMENT RESPONSE

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Introduction: The prediction of treatment response could save patients from long and complicated treatments and identify those who would benefit of an early definitive treatment. **Objectives:** Analyze the thyrotropin receptor antibodies (TRAb) and antithyroid peroxidase antibodies (ATPO) as predictors of treatment response and association with dermatopathy (DP) and/or Grave's ophthalmopathy (GO). **Material and methods:** Retrospective, observational study in which we studied 297 medical records of an Endocrinology Service following a research protocol approved by the Ethics and Research Committee. **Results:** A total of 207 patients were included, 82% female and 18% male. Among the 71 who achieved remission, 47% had negative TRAb and 30% had positive antibody levels in all exams, with a mean of 22.9 IU/L. In the group of 136 patients who relapsed only 27% had negative TRAb. The levels of TRAb were lower on the patients who achieved remission ($p = 0.049$). Of the patients who achieved remission, 54% had negative TRAb and 46% had positive TRAb at the time of drug withdrawal. Nine had subsequently recurrence, were 8 presented positive TRAb at the moment of withdrawal. In patients with positive TRAb at the time of remission, 44% had recurrence and among the ones with negative TRAb only 5% had recurrence. Analyzing the ATPO we noticed that 56% of those who achieved remission had a positive antibody, with a mean ATPO of 262.28 U/mL, lower than those with active disease, where the mean was 383,93 U/mL. Among those who did not achieve remission, 31% had negative ATPO during follow-up. Patients with and without remission did not present a significant difference in ATPO levels ($p = 0.60$). Among the patients with no remission, 69% presented positive ATPO, with no statistically significant difference for the remission group ($p = 0.32$). The mean TRAb in patients with GO (23.95 IU/L) was higher than in patients without (16.56 IU/L) ($p = 0.097$). The mean ATPO in patients with GO (429.99 U/mL) was higher than in patients without (295.63 U/mL) ($p = 0.048$). Patients with DP had a mean TRAb of 30.52 IU/L, higher than those who did not present skin changes 19.42 U/L ($p = 0.56$). The mean ATPO in patients with DP was 419.3 U/mL and without DP 333.98 ($p = 0.73$). **Conclusion:** The mean TRAb levels of the patients who achieved remission were lower than the levels of patients who did not ($p < 0.05$). In patients with GO, the mean ATPO was higher than in patients with no GO ($p < 0.05$).

56592 EVALUATION OF TRANSAMINASE LEVELS AND ASSOCIATION WITH TRAB AND ATPO IN PATIENTS WITH GRAVES' DISEASE

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Introduction: Changes in liver function tests are often seen in patients with Graves' disease. Recent studies have shown that elevation of thyrotropin receptor antibody (TRAb) may be an independent risk factor for elevation of transaminases, also TRAb and thyroid hormones are related to hepatic dysfunction. There is still a scarcity of data in the relationship between thyroid peroxidase antibodies (ATPO) and transaminases and factors contributing to such abnormalities in this patients. However, some studies show conflicting results. **Objectives:** Analyze the association of transaminase levels with TRAb and ATPO in patients with Graves' disease. **Material and methods:** Retrospective and observational study evaluating patients attended at an Endocrinology Service in Rio de Janeiro, 114 patients were included in the final statistical analysis. **Results:** In one hundred and fourteen patients evaluated, the mean TRAb was 20.61 IU/L. In this population the mean TGO/AST was 21.56 U/L. By evaluating those with TGO/AST above the reference value (mean 49.5 U/L) the mean TRAb was 15.48 IU/L, we did not observe higher values. TGP/ALT values were 22.36 U/L and TRAb 20.61 IU/L. The same occurred in patients who presented TGP/ALT above the reference values (mean 55.14 U/L), in which the levels of TRAb were also not elevated (mean 14 IU/L). In sixty-six patients who had ATPO dosed the mean was 391.4 IU/mL and that of TGO/AST was 25.11 U/L. The antithyroperoxidase antibodies were also not found to be higher (mean: 348.93 IU/mL) in the group of patients with a TGO/AST above the reference value (mean 65.33 U/L). The mean TGP/ALT levels were 22.88 U/L and ATPO 391.4 IU/mL [variation: 0.1 to 4320; (SD: 647.98)]. In that group of patients who had these enzymes elevated (mean 45.43 U/L) the titre of the ATPO was higher, 551.1 U/mL [variation: 8.70 to 3348.0; (SD: 828.63)] but not statistically significant ($p = 0.378$). **Conclusion:** There seems to be no relation between high levels of TGO/AST or TGP/ALT and TRAb. The result is in disagreement with some evidence such as a retrospective study in which 70.9% of the 289 patients presented transaminase alterations and higher levels of TRAb were found (22.2 *vs.* 17.4 IU/L, $P < 0.001$). Evaluating ATPO and transaminase levels, the results again suggest that there is no relationship between autoantibodies and levels of TGO. However, evaluating TGP/ALT we observed a higher mean ATPO in patients with TGP > 30 U/L although with no statistical significance ($p = 0.378$).

55914 GRAVES' ORBITOPATHY: RESPONSE TO SYSTEMIC GLUCOCORTICOID THERAPY, ITS RELATIONSHIP WITH TRAB LEVELS AND OTHER RISK FACTORS

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TSH receptor is the major autoantigen in Graves' disease; antibodies against it (TRAb) show a positive correlation with clinical characteristics of Graves' orbitopathy (GO) and influence prognosis, but the relation between evolution of TRAb levels and response to systemic glucocorticoid (SGC) therapy is unknown. Older age, male gender, thyroid dysfunction and smoking are others risk factors, but the relationship with response to treatment is not established. **Objectives:** 1) To analyze the response to treatment to SGC and classical risk factors for GO; 2) to evaluate evolution of TRAb levels after SGC and its relationship with response to treatment. **Methods:** Prospective study. Sixteen patients were included, 10 with severe GO and 6 at risk of vision loss. Median follow-up was 25 months (range 6-48). All of them were treated with SGC: 12 weekly infusions of methylprednisolone (500 mg/week for 6 weeks followed by 250 mg/week for 6 weeks) in sever GO or 1g of methylprednisolone for 3 consecutive days in risk of vision loss. Laboratory tests (TSH, T4, T3, ATPO, TRAb and 25OH vitamin D), were performed before treatment; TRAb was also measured within 3 and at 12 months after treatment. Satisfactory response was defined as resolution or improvement in activity/severity of GO and unsatisfactory response as stabilization without improvement or deterioration of GO. Both responses were compared to TRAb curve, risk factors and vitamin D levels. **Results:** 12 patients (75%) had a satisfactory response and 4 (25%) had an unsatisfactory response. No differences were found between the two treatment protocols and type of response. Patients with a satisfactory response had a tendency to lower baseline and 3 months TRAb levels (40.7 ± 24.2 *vs.* 66.5 ± 4.6% and 23.2 ± 20.3 *vs.* 51 ± 16%, $p = 0.06$); they also had a significant decrease in TRAb values within 3 months and one year after SGC therapy ($p < 0.05$), which was not observed in patients with an unsatisfactory response. No association was found between other risk factors and response to treatment. **Conclusions:** 1) Satisfactory response rate to SGC therapy was 75%, similar to what is reported in the literature; 2) basal TRAb levels were higher in patients with unsatisfactory response; 3) only patients with a satisfactory response had a significant decrease in TRAb levels after treatment. We consider that TRAb decrease within the first 3 months after treatment may be a marker of GO response to SGC therapy.

55897 SPONTANEOUS CONVERSION FROM HASHIMOTO THYROIDITIS TO GRAVE' DISEASE: A CASE REPORT

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Case: A 28-year-old female with hypothyroidism on levotyroxine (LT4) for > 15 years presented with 6 months of tachycardia, tremors, heat intolerance, weight gain and goiter. Her symptoms worsened despite change on LT4 dose. Laboratory tests showed TSH < 0,005 mIU/L, free T4 2,5 ng/dL and TRAb 4,9 IU/L. Thyroid ultrasound showed an increased and heterogeneous thyroid with high blood flow. Her symptoms and lab tests improved on methimazole and propranolol therapy. **Discussion:** Graves' disease and Hashimoto's thyroiditis are the two autoimmune spectrum of thyroid disease. Cases of conversion from hyperthyroidism to hypothyroidism have been reported but conversion from hypothyroidism to hyperthyroidism is very rare. It has been reported in patients who develop a relative predominance of thyroid-stimulating autoantibodies (TSAb) compared to TSH blocking autoantibodies (TBAb). These changes can also involve differences in TSAb *versus* TBAb affinities and/or potencies in individual patients. This phemomen has been described in situations of imune reconstitution, such as after HIV suppression and postpartum. Also, it has been described that LT4 therapy may alter dendritic and regulatory T cell function reducing TBAb and increasing TSAb. **Final comments**: Doctors should be aware that spontaneous conversion from Hashimoto thyroiditis to Grave's disease is possible even in a patient with longstanding, treated hypothyroidism. More studies are necessary to elucidate the physiology of this switch.

55740 VITILIGO AND HASHIMOTO'S THYROIDITIS - MOLECULAR MIMICRY: AN *IN SILICO* STUDY

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Introduction: Vitiligo is a multifactorial acquired depigmenting disorder, characterized by a spontaneous loss of functional melanocytes from the epidermis. Vitiligo and Hashimoto's thyroiditis (HT) often occur in association and seem to be characterized by an autoimmune process. The vitiligo associated with HT suggests genetic homologies between them. **Objective:** To identify protein sequence homology between melanocyte protein (Pmel) and thyroid peroxidase (TPO), using bioinformatics tools, to propose an initial mechanism which could explain the production of cross-reacting autoantibodies to melanocyte and TPO. **Methods:** We performed a comparison between Pmel and TPO amino acids (AA) sequences, available on the National Center for Biotechnology Information (NCBI) database by BLAST (Basic Local Alignment Search Tool) in order to find local homology regions between the AA sequences. **Results:** The homology sequence between the Pmel and TPO ranged from 21.0 % (19 identical residues out of 90 AA in the sequence) to 55.0% (6 identical residues out of 11 AA in the sequence) The structural alignments presented relatively high. **Conclusion:** Bioinformatics data suggest a possible pathological link between Pmel and TPO. Sequence homology between Pmel and TPO may present a molecular mimicry suggesting the possibility of antigen crossover between Pmel and TPO that might represent an immunological basis for vitiligo associated with HT.

THYROID CANCER BASIC

56658 C1ORF24 MEDIATES AUTOPHAGY IN THYROID CELL LINES

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Introduction: C1orf24, also known as Niban or FAM129A, was previously identified as one of the 4-gene panel of thyroid carcinomas markers. Although C1orf24 was also found highly expressed in several cancer subtypes such as renal, prostate and head and neck, its cellular function is still unknown. Interestingly, C1orf24 was upregulated in the Eker rat model of renal carcinogenesis, which had a germline mutation in rat homologue of human TSC2 gene, the main regulator of mTOR activation. Autophagy, an intracellular degradation process, is affected by mTOR status and has emerged as an essential mechanism to carcinogenesis. **Objectives:** To investigate whether C1orf24 regulates autophagy in thyroid cells. **Methods:** PC Cl3 normal thyroid cells were cultured in medium without serum, TSH and Insulin for 72 hours and then stimulated with serum and/or TSH and Insulin. The expression of C1orf24 and the LC3-I/LC3-II ratio, which is a hallmark of autophagy, was monitored by Western Blot analysis. Additionally, PC Cl3 were permanently transfected with vector expressing C1orf24, infected with mCherry-GFP-LC3 and the autophagic flux was analyzed by confocal microscopy. The effect of the ectopic expression of C1orf24 in PC Cl3 cells was also observed under transmission electron microscope (TEM). To further demonstrate the role of C1orf24 in autophagy, using a siRNA strategy, C1orf24 was silenced in a papillary thyroid carcinoma cell line (TPC1) that harbors RET/PTC1 fusion, and the rate of autophagy was monitored. **Results:** Withdraw of growth factors (TSH and Insulin) and serum from the complete medium was able to induce C1orf24 expression, as well as, to increase the conversion of LC3-I to LC3-II. When serum was added to the medium, together with TSH and Insulin, expression of C1orf24 returned to basal levels and rate of autophagy was reduced. Ectopic expression of C1orf24 in PC Cl3 cells increased autophagosome formation, indicated by yellow puncta formation in confocal microscopy. Intriguingly, autophagic flux was increased when C1orf24 was silenced in TPC1 cells. **Conclusion:** Our findings suggest that C1orf24 is an important player of starvation-induced autophagy in thyroid cells but how autophagy controls cell death seems to be dependent on the type and the genetic background of the cell.

56659 CARBOHYDRATE ANTIGEN 19.9 EXPRESSION IN TUMOR SAMPLES OF MEDULLARY THYROID CARCINOMA IS NOT ASSOCIATED WITH CELLULAR DEDIFFERENTIATION

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Introduction: Medullary thyroid carcinoma (MTC) is a rare malignant tumor originating from parafollicular C cells of the thyroid. Calcitonin and carcinoembryonic antigen (CEA) are widely used as MTC prognostic markers. Recent studies have suggested elevated serum levels of carbohydrate antigen 19.9 (CA 19.9), a well-established tumor marker in pancreatic neoplasms, as a marker of aggressiveness and mortality in advanced MTC. The mechanism by which MTC cells secrete Ca 19.9 has not yet been elucidated, but c-cell dedifferentiation has been suggested as a potential explanation. **Objective:** To evaluate CA 19.9 expression in MTC samples and correlate it with a cellular dedifferentiation, as well as clinical and laboratory data. **Methods:** MTC tumor samples from patients attending the Thyroid Division of a tertiary, University-based Hospital were evaluated for CA 19.9 and CD-133 expression by immunohistochemistry using specific antibodies. The slide reading was performed by a pathologist and the quantification by the h-score method. **Results:** MTC tumor specimens from 65 patients were evaluated (43.1% hereditary and 56.9% sporadic). The mean age at diagnosis was 36.02 ± 16.37 years, and 56.9% were female. The median levels of calcitonin and CEA were 527 pg/ml (42.5-1168.7) and 16.1 ng/ml (3-49.65), respectively. At diagnosis, 53.8% of the patients had local, and 21.5% had distant metastases. Some level of CA 19.9 expression was observed in 86.2% of samples, and the median of the h-score was 13 (2-30). CD-133 expression was seen in ~90% of samples analyzed (h-score = 40; 3-120). Of note, despite the positivity of both markers in most of the samples, the h-score values were not correlated (p = 0.78). There were no difference in the expression of CA 19.9 on age, sex, calcitonin and CEA values, calcitonin tissue expression or tumor staging (All P > 0.05). However, interestingly, we observed a significant difference between the h-scores in the hereditary *vs.* sporadic form (23.5 *vs.* 3; P = 0.017). **Conclusion:** Our results demonstrate CA 19.9 and CD-133 expression in the vast majority of CMT samples, including small tumors in early stages of the disease. Higher levels of CA 19.9 expression were observed in hereditary MTC as compared with those with sporadic disease. However, CA 19.9 expression was not associated with cell dedifferentiation nor advanced MTC disease.

56563 CLINICAL AND ANATOMOPATHOLOGICAL CHARACTERISTICS OF DIFFERENTIATED THYROID CANCER

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Introduction: Differentiated thyroid carcinoma is the most frequent endocrine neoplasia, showing an increasing incidence. It is a tumor of favorable course with survivals around 85%-90%. However, there are cases of more aggressive behavior with local recurrences or the appearance of distant metastases, so it is important to know the characteristics of the same and establish the risk of initial recurrence to assess treatment and follow-up. **Objective:** To describe the clinical and anatomopathological characteristics of differentiated thyroid carcinoma of patients surgically operated at the Central Hospital of the Institute of Social Prevision.in the period from January 2011 to December 2015. **Methods:** Observational, descriptive, retrospective cross-sectional study. **Results:** A total of 764 pathologic clinical files were reviewed, and 21.85% were differentiated thyroid carcinomas. Female gender 90.00%, ratio 9: 1, mean age 47 ± 15 years, from the Paraguay central department 74.25%. The most frequent histological type was papillary carcinoma, 89.00%. Most common morphological alteration was multinodular goiter 66.00%. Total thyroidectomy was the initial treatment 73.00%. Tumor size and invasions were found greater number of patients between 1 and 4 cm evidencing vascular invasion in this group. 30.00% multifocality was observed. Risk of initial recurrence according to the criteria of the American Thyroid Association 2015 was intermediate in 64.67%, low 24, 55% and high risk 10, 77%. **Conclusion:** The predominant histological type was conventional papillary carcinoma. The most frequent morphological alteration was multinodular goiter. The initial treatment was total thyroidectomy. Increased numbers of capsular, vascular and lymph node invasions were observed as tumor size increased. It was found that more than a third of the population studied had tumor multifocality and that it was related to size. A minimal percentage of surgical reintervention was evidenced. Prevalence of intermediate recurrence risk according to ATA 2015 criteria was observed.

55806 COULD THE EXPRESSION OF TGFB1, TGFBR1 AND TGFBR2 GENES BE USEFUL IN THE DIAGNOSIS OF THYROID MALIGNANCY?

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Introduction: Thyroid nodules are extremely frequent in the population; establishing a precise and fast diagnosis is still a challenge in clinical practice. TGF-β1 is an important cytokine involved in proliferation, migration, cell differentiation and apoptosis, as well as an important regulator of the immune system, mediating intracellular activations of proinflammatory cytokines. Immune cells are often found in differentiated thyroid carcinoma and the immune response against tumor cells is able to influence the prognosis of the patient. **Objective:** The aim of this study was to investigate the role of TGFB1, TGFBR1 and TGFBR2 genes as tumor markers of thyroid malignancy. **Material and methods:** We analyzed RNA samples that were submitted to RT-PCR technique, followed by mRNA quantification by qPCR of 30 malignant nodules, 24 benign nodules and 14 normal tissues. Results The expression of TGFB1 was higher in malignant than in benign nodules (means 2,490 ± 1.650 AU and 0.677 ± 0.437 AU, respectively), hence identifying malignancy with an accuracy of 92% ($p < 0.0001$), specificity of 95% and negative predictive value (NPV) of 99% (95% CI: 16.9-75.6); the sensibility and positive predictive value (PPV) of this test were 79% and 44% (95% CI: 97.7-99.4), respectively. Likewise, the expression of TGFBR1 was higher in malignant than in benign nodules (1.678 ± 1.525 AU *versus* 0.316 ± 0.221 AU respectively), identifying malignancy with a specificity of 100%, NPV of 97%, sensibility of 50% and PPV of 100%, showing an accuracy of 80% ($p < 0.0001$). The TGFBR2 expression was also different in the malignant and benign groups ($p = 0.0017$); however did not demonstrate efficacy for the diagnosis ($p = 0.7218$). Concerning patients' clinical characteristics, TGFBR1 expression was lower in encapsulated tumors (0.666 ± 0.291 AU) than the not encapsulated tumors (1.808 ± 1.392 AU) ($p = 0.0191$); however, no other clinical characteristics were associated with the expression of the genes investigated. **Conclusion:** These preliminary data corroborate others available in the literature and suggest that the evaluation of TGFB1 and TGFBR1, but not TGFBR2 gene expression may be a useful marker of thyroid nodules malignancy.

56671 DISCOVERY OF NOVEL SPORADIC GENETIC EVENT INVOLVING THE RET GENE IN PHEOCHROMOCYTOMA AND MEDULLARY THYROID CARCINOMA

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Introduction: Multiple endocrine neoplasia type 2 (MEN 2) is associated with high risk of developing medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO), and parathyroid adenoma or hyperplasia. Depending on the tissues involved, it can be divided into MEN 2A or MEN 2B. This autosomal-dominant hereditary syndrome is caused by germline mutations in the RET gene. Somatic mutations in the RET gene have also been associated with sporadic MTC. It has been suggest that a second-hit mutation at the RET locus might be associated with the pathogenesis of MTC and PHEO. In this study we explored the presence of somatic second hit mutations in the RET gene in sporadic and hereditary MTC and PHEO. **Methods:** DNA was extracted from paraffin-embedded sporadic and MEN 2-associated MTC (n = 38) and PHEO (n = 23) samples, which were selected from the files of the Department of Pathology of the Federal University of Sao Paulo, Brazil. Additionally, DNA from peripheral blood leukocytes of patients with hereditary MTC (n = 6) and papillary thyroid carcinomas samples (n = 10) were tested. Mutation screening in the RET gene was performed by direct DNA sequencing of PCR products. Multiplex Ligation-dependent Probe Amplification (MLPA) was used for the detection of RET copy number variation in genomic sequences. **Results:** We identified a somatic second-hit event involving the RET gene in both sporadic and Hereditary MTC and PHEO. MLPA probes, which span all RET exons, showed up to 3 fold amplification of several exons of the gene in both MTC and PHEO, while it was not detected in normal tissue or peripheral blood DNA from the same patients or PTC samples. We have also found that nearly 25% of MTC and 48% of PHEO were positive for a specific mutation in exon 8 of the RET gene (p.G548V). Interestingly, this new mutation is not present in the parental copy of the gene but is particularly present in the additional copies of the RET gene. **Conclusion:** We here describe a new somatic genetic event involving the RET gene in sporadic and hereditary MTC and PHEO. Further studies are needed to understand the mechanisms that originated this event and whether it has any implication in the pathogenesis of MTC and PHEO.

56696 EXTRACELLULAR VESICLES AS CARRIERS OF CD147 IN THYROID TUMOR MICROENVIRONMENT

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Introduction: The influence of tumor-stromal crosstalk on tumor progression is recognized in different types of cancer. Tumor-secreted extracellular vesicles (EVs) act as intercellular messengers between tumor and stromal cells in local and distant microenvironments. The mechanisms by which tumor cells establish a permissive microenvironment that promotes thyroid cancer progression remain largely undefined. CD147 is a transmembrane glycoprotein that induces matrix metalloproteinases (MMPs) expression. CD147 level correlates with the dedifferentiation-degree of thyroid cancer and has also been suggested as a significant prognostic factor in differentiated thyroid carcinomas. In preliminary studies, we found that thyroid tumor cell-fibroblasts (Fb) interaction promotes the secretion and activation of MMPs and tumor cell migration. **Objectives:** To identify EVs production and their CD147 expression as potential features of thyroid tumor malignant progression in a model of tumor-stroma cell interaction. **Methods:** As an *in vitro* tumor-stroma cell interaction model, non-tumor cells (N-ThyOri), thyroid papillary carcinoma cells (TPC-1) and thyroid anaplastic cells (8505c) were co-cultured with normal Fb. EVs were isolated from conditioned media (CMs) by differential centrifugation and filtration steps. EVs ultrastructural features, and EVs sizes and populations in co-cultured and isolated cells were characterized by Transmission Electronic Microscopy (TEM) and Dynamic Light Scattering. CD147 expression was analyzed by western blotting and immunogold labeling in EVs, and by indirect immunofluorescence in whole cells. **Results:** Cell membrane periphery of thyroid cell-Fb co-cultures was rich in both round and villi-like membrane projections. In contrast, TEM analysis of normal Fb or isolated thyroid cells revealed a smoother cell surface. Isolated EVs from CMs ranged between 50-600 nm. The CD147 protein in EVs from CMs evidenced a higher expression in TPC-1-Fb and 8505c-Fb co-cultures when compared to N-ThyOri-Fb co-cultures. By immunofluorescence, CD147 expression in whole tumor thyroid cells displayed a dotted pattern during thyroid tumor cell-Fb co-culture. **Conclusion:** The results suggest that CD147 could play an active role in intercellular communication events in thyroid-tumor microenvironment, stimulating the release of MMPs by cells in this environment and the consequent migration and cellular invasion.

56666 IDENTIFICATION OF BRAF FUSIONS IN PEDIATRIC PAPILLARY THYROID CARCINOMA

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Introduction: The incidence of thyroid carcinoma, mainly of the papillary histological subtype (PTC), has increased in most populations, including pediatric patients. Genetic alterations leading to the MAPK pathway activation are highly prevalent in PTC. It has been demonstrated that BRAF V600E mutation is the most prevalent mutation found in adult sporadic PTC, with a worldwide prevalence of ~40%. However, the BRAF V600E mutation is rarely identified in pediatric PTC. In contrast, chromosomal rearrangements involving BRAF gene have been identified mainly in radiation-exposed pediatric PTC. We recently described, for the first time in the literature, the presence of AGK-BRAF fusion in 3/30 (10%) of sporadic pediatric PTC, suggesting that it might be an alternative mechanism of aberrant BRAF activation in pediatric cases. **Objectives:** The present work aimed to investigate rearrangements involving BRAF in a large multicenter cohort of pediatric PTC (< 18 years old) and correlate the mutational status with clinicopathological features. **Methods:** The AGK-BRAF rearrangement was screened in 55 pediatric PTC, using the RT-PCR and sequencing techniques. As BRAF rearrangements can also involve non-AKG partners, in the AGK-BRAF negative cases, we used BRAF FISH break-apart to screen for additional fusions involving BRAF gene. Next, 5I Rapid Amplification of cDNA Ends (5 RACE) was used to identify the fusion partners. **Results:** AGK-BRAF was found in over 20% of pediatric sporadic cases. Two additional BRAF-rearranged cases were identified using BRAF FISH break-apart and 5RRACE strategy. Extrathyroidal extension was observed in all patients with AGK-BRAF rearrangement. Eight of nine (89%) tumors positive for AGK-BRAF had lymph node metastasis at diagnosis, whereas distant metastases were identified in 6/9 (67%) tumors with this rearrangement. **Conclusion:** A high prevalence of rearrangements involving BRAF gene was identified in pediatric PTC, being the AGK gene the most prevalent partner gene. A trend toward a more aggressive phenotype was observed in BRAF-positive cases. We believe that our findings improved understanding of the molecular basis of thyroid carcinomas in the pediatric population and, ultimately, will help preoperative diagnosis and prognosis.

55559 *IN SILICO* PROJECTION OF MOLECULAR STRUCTURE OF MICRORNA INHIBITORS AGAINST MICRORNA OVER-EXPRESSED IN THYROID CANCER

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Introduction: Thyroid cancer is the most prevalent malignant neoplasm of endocrine system and advances in thyroid molecular biology studies demonstrate that microRNAs (miRNAs) seem to play a fundamental role in tumor triggering and progression. The miRNAs inhibitors are nucleic acid-based molecules that blockade miRNAs function, making unavailable for develop their usual function, also acting as gene expression controlling molecules. **Objective:** To develop *in silico* projection of molecular structure of miRNA inhibitors against miRNA over-expressed in thyroid cancer. **Methods:** We conducted a search of the nucleotide sequence of 12 miRNAs already defined as inhibitors against miRNA over-expressed in thyroid cancer, realizing *in silico* projection of the molecular structure of following miRNAs: miRNA-101, miRNA-126, miRNA-126-3p, miRNA-141, miRNA-145, miRNA-146b, miRNA-206, miRNA-3666, miRNA-497, miRNA-539, miRNA-613, and miRNA-618. The nucleotides were selected using GenBank that is the NIH genetic sequence database. The sequences obtained were aligned with the Clustal W multiple alignment algorithms. For the molecular modeling, the structures were generated with the RNAstructure, a fully automated miRNAs structure modelling server, accessible via the Web Servers for RNA Secondary Structure Prediction. **Results:** We demonstrated a search for nucleotide sequence and the projection of the molecular structure of the following miRNA inhibitors against miRNA over-expressed in thyroid cancer: miRNA-101, miRNA-126, miRNA-126-3p, miRNA-141, miRNA-145, miRNA-146b, miRNA-206, miRNA-3666, miRNA-497, miRNA-539, miRNA-613, and miRNA-618. **Conclusion:** In this study we show *in silico* secondary structures projection of selected of 12 miRNA inhibitors against miRNA over-expressed in thyroid cancer through computational biology.

56171 MOLECULAR ABNORMALITIES IN THYROID TUMORS OCCURRING AFTER EXPOSURE TO EXTERNAL RADIATION

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Introduction: Thyroid gland is highly sensitive to the carcinogenic effects of ionizing radiation. The risk increases with higher radiation doses delivered to the thyroid gland and with younger age at exposure. Current data suggest that radiation induced tumors may have some specific clinical, histopathological or molecular characteristics. The aim of this work is to evaluate which differences could contribute to the characterization of radiation-induced thyroid nodules. **Materials and methods:** 41 thyroid tumors [19 adenomas and 22 differentiated thyroid carcinomas (DTC)], that occurred in patients with a history of radiation therapy and 51 control cases (24 adenomas and 27 Carcinomas) were analyzed using the Ion Torrent™ Oncomine™ Focus Assay in a multibiomarker next-generation high-throughput sequencing assay. **Results:** Median age at radiation exposure was 10 years and median age at thyroid nodule diagnosis was 31 years (range 12-71). Papillary thyroid carcinoma (PTC) was the most frequent histology in both groups (18/22 radiation exposed and 27/27 sporadic carcinomas). There was no difference in histopathologic features between sporadic and radiation-exposed PTC cases. A total of 43 genetic abnormalities were identified, consisting in 25 fusions and 18 point mutations (BRAF, HRAS & NRAS hotspot mutations). In the radiation-exposed cohort, among the 19 adenomas 1 fusion was identified, and in the 22 DTCs 12 fusions and 2 point mutations were detected. In the sporadic cohort, in the 24 adenomas, 1 fusion and 6 point mutations were detected and among the 27 carcinomas 11 fusions and 10 point mutations were identified. RET/PTC1 (n = 6) and RET/PTC3 (n = 7) were the most frequent fusion transcripts detected in DTCs, followed by ETV6/NTRK3 (n = 6). We identified the fusion KIAA1468 (10)/RET (12) in 2 radiation-exposed samples. This fusion has not been previously reported. **Conclusion:** Sporadic and radio-exposed nodules present similar clinical behaviour, histopathologic features and hotspot molecular abnormalities. Point mutations were found mostly in sporadic cases. Current research is directed on the extensive analysis by whole transcriptome sequencing to identify a molecular signature that can predict the origin of a thyroid tumor after a known or a suspected exposure to ionizing radiation.

56611 OPNA VARIANT EXPRESSION IS ASSOCIATED WITH CALCIFICATION IN THYROID CANCER CELL LINE

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Introduction: Osteopontin (OPN) and its three spliced variants (OPN-SV: OPNa, OPNb and OPNc) are overexpressed in several tumors and frequently associated with cancer progression. This holds true for papillary thyroid carcinoma (PTC) which is the most common variety of thyroid cancer (TC) being the histologic type which often presents desmoplasia (collagen deposition) and dystrophic calcification, including a fairly typical feature, the psammoma bodies (PB). **Objective:** The aim of this study was to investigate the role of OPN-SV expression in the calcification and in classical variant of PTC (cPTC). **Methods:** Total OPN and OPN-SV expression was analyzed by immunohistochemistry and real time PCR in a series of 48 cPTC cases and three diffuse sclerosing PTCs. The association of OPN expression and the presence of PB as well as between PB in cPTC and the clinicopathological features of the tumors were evaluated. TPC-1 and c643 TC cell lines overexpressing OPN-SV were tested for the ability to promote calcification and to synthesize collagen *in vitro.* **Results:** Overexpression of OPNa transcripts was significantly associated with the presence of PB in cPTC samples. The presence of PB in cPTC was associated with younger patients and lymph node metastasis. Moreover, OPNa overexpression displayed a strong capacity to promote calcification and substantial collagen synthesis in thyroid cancer cell lines. **Conclusion:** Our data suggest that OPNa plays a role in the formation of calcification often associated with cPTC. Basic research on the interactions between OPNa overexpression by tumor cells and the surrounding microenvironment can give clues for a better understanding of cPTC biology and phenotype.

56705 OUABAIN EFFECTS ON HUMAN THYROID CARCINOMA CELL LINES

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Introduction: Ouabain was initially described as a compound extracted from plants; capable of binding to Na+, K+-ATPase and inhibiting Na+ and K+ transport. Following the inhibition of ion transport, intracellular Na+ levels increase, Na+/Ca2+ exchanger reverse and intracellular Ca2+ levels increase. Due to its positive ionotropic effect on cardiac muscle, ouabain was used for the treatment of cardiac dysfunctions. In 1991, an endogenous analogue of ouabain was discovered. Nowadays, many authors believe that ouabain is also a stress-related hormone, produced by adrenal glands and hypothalamus. Numerous effects of ouabain have been described. These include: the inhibition of mitogen-induced lymphocyte proliferation; the modulation of cytokine secretion by mononuclear cells; the modulation of histiocytic lymphoma-derived cells viability; and the reduction of the migratory ability of lung cancer cells. **Objective:** The aim of this work was to evaluate the effect of ouabain on the biology of human thyroid cancer cells, in order to verify a possible antitumoral role of this molecule in thyroid carcinoma. **Methods:** In this work, we used four human thyroid cell lines: 8505C, an undifferentiated thyroid carcinoma-derived cell line; BCPAP, a papillary thyroid carcinoma-derived cell line with BRAFv600e mutation; TPC-1, a papillary thyroid carcinoma-derived cell line with RET/PTC translocation; and NTHY-ori, a non-tumoral cell line. Cells were cultured in the presence or absence of ouabain, at different concentrations. Subsequently, we evaluated the effect of ouabain on the viability and migratory ability of these cell lines. **Results and conclusion:** All ouabain-treated cultures showed a reduced percentage of viable cells when compared to control cultures after 24 hours. Moreover, preliminary results suggest that ouabain appears to be able to impair TPC-1 migration *in vitro.* Therefore, our results indicate 10-7M of ouabain, a concentration that can be found in the plasma of patients treated with ouabain in clinical setups or in individuals under stress, may have a promising antitumoral effect in thyroid carcinoma.

55140 PREVALENCE OF MOLECULAR MARKERS – TERT, BRAF AND RAS – AND THEIR IMPACT ON THE OUTCOME IN THE SPECIFIC SUBGROUP OF THE AGGRESSIVE HISTOLOGICAL VARIANTS OF THE THYROID CARCINOMA DERIVED FROM FOLLICULAR CELLS

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Introduction: The role of the mutations TERT, BRAF and RAS in the specific subgroup of the aggressive histological variants of the thyroid carcinoma derived from follicular cells (TCDFC) is not well defined. **Objective:** To evaluate the frequency and impact on the outcome of TERT, RAS and BRAF mutations in 49 patients with TCDFC with aggressive histology. **Methods:** Analysis of the presence of TERT (C228T;-124C>T and C250T;-146>T), BRAF (V600E) and RAS (Q 61R) mutations by the genomic sequencing of DNA samples from thyroid tumors extracted from paraffin blocks and analysis of their correlation with the outcome of the patients collected from the medical records database. **Results:** Median age at diagnosis was 62 years, 71,4% were female, median primary tumor size of 4 cm, 51% were N1 and 51% M1, 81,6% and 18,4% were high and intermediate risk (2015 ATA) respectively, all of them had tumors with histopathology aggressive (aggressive variants of PTC 67,3%; insular/PDTC 20,5% invasive FTC and Hurthle cell variant 12,2%). RAI was performed in 79,6%. The response to the initial therapy was excellent in 42,8% and structural incomplete in 49%. During the follow-up period (median 72 months; 5-360 months) 46,9% presented disease progression and 20,4% disease related death. 55% showed at least one molecular alteration and six patients had two or more (TERT in 34,7%; BRAF in 24.5%; RAS in 12.24%). In univariate analisys, factors associated with poor response to initial therapy were ATA risk high ($p < 0.001$), a higher proportion of PDTC/insular and FTC in structural incomplete response group ($p = 0.005$), distant metastasis at diagnosis ($p = 0.004$), TERT mutation ($p = 0.001$), BRAF mutation ($p = 0.03$) and NRAS mutation ($p = 0.008$). Also in a univariate analysis none of these possible predictor of structural disease progression were associated significantly with this progression. In a multivariate analysis TERT mutation remain significantly associated with the risk of having structural disease after initial therapy ($p = 0,01$), as well as the presence of distant metastasis ($p = 0,04$) and RAS mutation ($p = 0,03$) and being ATA high risk ($p = 0,03$) whereas while the presence of BRAF mutation and histology were not significant. **Conclusions:** Among the three mutations evaluated the mutation of the TERT promoter gene was the most prevalent and was associated with the risk of having structural disease but not with the risk of progression in this specific subgroup of TCDFC with aggressive histology.

56675 REACTIVATION OF EMBRYONIC SIGNALING IN AGGRESSIVE THYROID CANCER CELL LINES

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Introduction: Thyroid cancer oncogenesis is associated with high prevalence of MAPK signaling genetic alterations such as mutations in BRAF and RAS genes, mainly in papillary thyroid cancer (PTC). These mutations are also observed in aggressive radioiodine-refractory papillary and anaplastic thyroid cancer (ATC), which frequently harbors mutations in TP53 and in PI3K signaling. However, the activation of additional signaling pathways in aggressive thyroid cancer is still not fully understood. The progressive loss of thyroid differentiation (i.e. inability to trap iodine and produce thyroid hormones) could be associated with activation of epithelial-mesenchymal transition (EMT) and acquisition of stem cell-like phenotype. Indeed, some studies point to the enrichment of stem cell markers in ATC, but the role of embryonic signaling reactivation in thyroid cancer remains elusive. **Objective:** The aim of this study was to evaluate the activation of embryonic signaling pathways in thyroid cancer. **Material and methods:** Total protein was extracted from three papillary (TPC-1, BCPAP, K1) and six anaplastic thyroid cancer cell lines (KTC2, SW1736, C643, Hth7, Hth74, Hth83). Total protein (30-40µg) was separated in 10% SDS-PAGE and blotted onto nitrocellulose membrane. NODAL, LIN28B, YAP1 and vimentin protein expression was detected using specific primary antibodies. After secondary HRP antibody incubation, membranes were incubated with ECL and chemoluminescence was detected in LAS4000 (GE Healthcare). Band intensity was analyzed by ImageJ and β-actin protein level was used as loading control. **Results:** NODAL protein was highly expressed in 5 out of 6 ATC cell lines, essentially in Hth74 and C643, when comparing to the PTC cell lines that showed lower expression. In addition, the expression of vimentin, a mesenchymal marker, was also high in ATC, preferentially in Hth74, Hth7 and C643, but was also detected in PTC, with the lowest levels presented by TPC-1 cells. To the same extent, YAP1 protein was detected preferentially in ATC cell lines (3 out of 6), mainly in Hth83, with faint bands in PTC cell lines. On the other hand, LIN28B was detected in Hth7 and KTC2 ATC cell lines, while not detected in other cell lines. **Conclusion:** In this study, we showed that embryonic NODAL, LIN28 and YAP signaling are reactivated in anaplastic thyroid cancer, along with EMT marker vimentin, indicating an important role for these pathways in the aggressiveness of thyroid cancer.

56629 RESPONSE TO TKI TREATMENT ACCORDING TO MOLECULAR STATUS IN ADVANCED MEDULLARY THYROID CARCINOMA

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Introduction: RET mutations are detected in hereditary (100%) and sporadic (50%) medullary thyroid carcinoma (MTC) and RAS mutation is found in up to 43% of sporadic tumors in the absence of RET mutation. Tyrosine kinase inhibitors (TKI) directed against RET tyrosine kinase are used in progressive metastatic or locally advanced MTC. We report the molecular status and the response to TKI treatment in a series of 50 patients with metastatic MTC. **Material and methods:** Germinal and somatic RET (exon 11-16), KRAS, HRAS, NRAS (exon 2-4) mutational status were tested in primitive tumor or metastatic tissue by Next Generation Sequencing (NGS). All patients had a progressive metastatic MTC and were treated with TKI (Vandetanib, Cabozantinib, Motesanib, Lenvatinib, Sunitinib, Sorafenib, Nindetanib, Lucitanib), from 2005 to 2016; 38% of patients received a 2nd line TKI therapy. **Results:** Patients were mostly men (74%), with a sporadic pattern (76%). Mean age at diagnosis was 46 yrs., and 70% had TNM stage IVa-IVc. At initiation of TKI treatment, 64% of patients had 3 or more metastatic sites and 92% had WHO performance status (PS) 0-1. RET mutation was detected in 42 cases (84%), RAS mutation in 6 (12%) and 3 samples (6%) were RET and RAS wt. PFS at 1 year for RET918 (21 cases), RET634 (9 cases), RET833 (1 case), other RET mutations (11 cases), RAS mutation and wt was 90% (95% CI 78%-100%), 75% (95% CI 50%-100%), 100%, 19% (95% CI 49-100%), 100% and 100%, respectively. Progression-free survival (PFS) at 1 year was 86% (95% CI 70%-97%) for 1st line TKI therapy and 52% (95% CI 30%-80%) for 2nd line therapy. In 1st line, 3 cases (6%) presented complete response (CR) and 18 (36%) partial response (PR). In 2nd line therapy, only 4 cases achieved PR (21%). With vandetanib as 1st line treatment in 36 cases, 3 CRs (9%) and 11 PRs (30%) were observed. With vandetanib as 2nd line therapy in 10 patients, 3 (30%) PR were observed. With cabozantinib as 1st line treatment in 7 patients and as the 2nd line in 2, 4 PR (57%) and 1 PR were observed, respectively. **Conclusion:** The prevalence of RET mutation in this series of 50 metastatic MTC patients is higher than previously reported. Longer PFS at one year was associated with several mutations. Second line TKI treatment is effective in some patients who progressed on first line treatment.

56683 ROLE OF NADPH OXIDASE DUOX1 IN THYROID RADIO-CARCINOGENESIS

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Introduction: RET translocations are a major cause of papillary thyroid carcinomas. RET/PTC1, the translocation between the genes RET and CCDC6, has been experimentally associated with radiation exposure and other genotoxic stressor, like reactive oxygen species (ROS). Interestingly, both RET and CCDC6 have been mapped to fragile sites, regions of the genome that are particularly sensitive to replicative stress. Ionizing radiation is also known to cause persistent effects on irradiated cells progeny, notably a persistent oxidative stress mediated by the upregulation of the NADPH Oxidase DUOX1 several days after the irradiation. However, the role of DUOX1-derived ROS on RET/PTC1 formation and fragile sites stability in the thyroid remains unknown. **Objectives:** Investigate whether irradiation of thyroid cells can elicit a replicative stress condition, if the replicative stress is related to RET/PTC1 formation and if DUOX1-derived ROS is involved in those processes. **Methods:** Non-tumoral human epithelial thyroid cell lineage NTHY-ori3.1 (SV-40 transformed) was used in all experiments and irradiated with 5 Gy using a X-Ray generator operating at 320KV (1 Gy/min). **Results:** Increased intra- and extracellular ROS production was observed in NTHY cells 3-4 days after a single 5 Gy-irradiation, accompanied by an increase in H2AX protein levels. However, virtually no effect was observed in cell proliferation, as measured by BrDU-incorporation and IP-based cell cycle analysis. Replicative stress markers such as pChk1, pATR and pATM were increased 72h after irradiation and their activations were partially reversed by antioxidants, suggesting a role for ROS in the onset of replicative stress. Moreover, the replicative stress hallmarks pRPA/H2AX and FANCD2/H2AX merged foci detected by immunofluorescence were highly increased in irradiated cells. Finally, replication dynamics analyzed by DNA combing shows that global replication speed is slightly diminished after irradiation, effect that have been reversed by short-term antioxidant (DPI) treatment. **Conclusion:** Our results suggest that irradiated cells are under a mild replicative stress stimulated by the increased ROS production, but more experiments are needed to reveal whether this condition can lead to RET/PTC1 formation and if DUOX1 is involved in those processes.

56680 ROLE OF NADPH OXIDASE NOX4 IN THE REDOX REGULATION OF THE SODIUM (NA+)/IODIDE (I-) SYMPORTER IN PAPILLARY THYROID CANCER

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Introduction: BRAFV600E contributes to the aggressiveness of papillary thyroid cancers (PTC) with altered expression of the sodium/iodide symporter (NIS), which is crucial for the treatment of patients with radioiodine. Our recent data highlight that the inactivation of the NADPH oxidase NOX4, a ROS generating system, promotes the reexpression of NIS in BRAFV600E--mutated thyroid cancer cell lines. The reversible nature of this inhibition raised the question whether NOX4 could regulate epigenetic modifications in the promoter region of the gene SCL5A5 (NIS). Indeed, it has been demonstrated that oxidative stress induces re-localization of a protein complex containing DNA methyl-transferases (DNMT) and histone deacetylase (HDAC) resulting in cancer-specific aberrant DNA methylation and transcriptional silencing of certain genes. Our hypothesis is that the recruitment of a silencing complex containing DNMTs and HDACs following NOX4-mediated DNA damage, over the NIS promoter, may inhibit its transcription. **Methods and Results:** By cell fractionation we show in the human PTC BRAFV600E-mutated cell line BCPAP that treatment with H2O2 results in enrichment in DNMT1 in tight-chromatin protein fraction which was decreased by antioxydants [diphenyliodonium (DPI), N-acetyl-L-cysteine]. NOX4 siRNA inactivation reduced DNMT1 protein both in whole cell lysates and chromatin-enriched fraction. We have previously demonstrated that NOX4 is a key effector of TGFβ. So we tested the effect of TGFβ treatment in BCPAP cells and also observed an increase in DNMT1 protein levels in chromatin fraction which was reversed by DPI treatment. In addition, we show that a nuclear-specific HDAC inhibitor (MS-275) strongly increases NIS expression in the BRAFV600E-mutated cell lines BCPAP and 8505C. Interestingly this is associated with NOX4 decreased mRNA levels in BCPAP cells. The work is now in progress. Further chromatin immunoprecipitation experiments will test the role of DNMT1 and HDAC1 in the regulation of NIS expression under the control of NOX4. **Conclusions:** The data obtained should lead to a better understanding of the mechanisms by which NOX4 controls the expression of NIS in thyroid tumor cells and bring functional data for the development of new tools of diagnosis and/or prognosis.

56573 CINTILOGRAPHIC MAPPING OF LYMPHATIC DRAINING OF THYROID WITH NANOCOLLOID IN PATIENTS SUBMITTED TO PARTIAL THYROIDECTOMY

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Introduction: Despite the high prevalence of regional metastases (25%-90%), papillary thyroid carcinoma (PTC) has a good prognosis, but the risk of relapse is not negligible, 5% to 20% of patients present recurrences. Total thyroidectomy is the surgical procedure of choice in patients with PTC, but several authors recommend elective central compartment dissection in patients with no evidence of lymph node involvement. A distinct form of dissemination, skip metastasis involving the lateral compartment can occur in up to 38% of patients. The lymphatic drainage (LD) of the thyroid can present great variations, the knowledge of it can prevent a surgical intervention extensive or insufficient. **Objective:** Understand the LD of the thyroid in its different regions through lymphoscintigraphy for try to understand the skip metastasis and the metastatic spread of PTC. **Methods:** This study is being carried out at the Marília Medical School, with the support of the São Paulo Research Foundation (Fapesp), (Ethics Committee 29172914.7.0000.5413). Patients older than 18 years, with prior indication of partial thyroidectomy, and who agree to participate in the study are included. During the partial thyroidectomy, the radiocolloid is injected in the remaining lobe, in UPPER and LOWER groups. After surgery, patients undergo lymphoscintigraphy in dual-head gamma, static images are obtained in the anterior and lateral projections, it is possible to observe the LD and the number of lymph nodes. During lymphoscintigraphy, the patient's neck is photographed for comparison. **Results:** According to the results of lymphoscintigraphy, patients were separated into 3 groups: not drain, drained only to level VI and drained to level VI and lateral level. In the 23 patients performed, 48% drained to level VI and lateral level (UPPER, 30.5% and LOWER, 17.4%), 30.4% drained only to level VI (13% and 17,4%) and 21.6% did not drain (13% e 8,7%). The levels that received the most drainage were, level VI – 18 patients. Level II – 10 patients, level III – 3 patients, level IV – 5 patients. Of the 18 patients who drained to level VI, in 14 patients (77.8%) drainage was unilateral and only in 4 patients (22.2%). **Conclusions:** The LD of the thyroid is complex and diverse. Level VI is the level that receives the most drainage, however it is very common to drain to lateral levels. The LD is preferably unilateral and possibly bilateral, at level VI. Lateral levels analyze carefully in patients with PTC.

THYROID CANCER CLINICAL

55782 COMPARISON OF INITIAL RESPONSE TO TREATMENT AFTER REMNANT ABLATION (RA) WITH 30 MCI OF 131-I *VERSUS* NO RA IN PATIENTS WITH DIFFERENTIATED THYROID CANCER WITH LOW RISK OF RECURRENCE. MULTICENTRIC PROSPECTIVE STUDY*

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* Performed with members of the Thyroid Department from the Sociedad Argentina de Endocrinología y Metabolismo.

Introduction: The therapeutic approach of patients with differentiated thyroid cancer (DTC) is currently individualized according to the risk of recurrence, with a lower tendency to perform remnant ablation (RA). RA did not demonstrate to reduce mortality or prolong disease-free survival, although it could probably facilitate the follow-up. The objective of this prospective, multicentric study was to compare the initial response to treatment in two groups of low risk patients categorized according to the classification of the Argentine Intersocietary Consensus, one of them ablated with 30 mCi of I^{131} and the other one without RA. **Patients and methods:** We included 174 patients; 87 patients in each of the groups (ablated and non-ablated). The evaluation of the response to treatment was performed with thyroglobulin and anti-thyroglobulin antibodies measurement and neck ultrasonography. **Results:** The baseline characteristics of both groups were compared, and no statistically significant differences were found: female sex 84% and 88.5%, respectively, ($p = 0.5$); mean age of 46.8 and 47.5 years, respectively ($p = 0.7$); papillary carcinoma classic variant 68% and 75.9%, respectively ($p = 0.15$). The rest of the baseline characteristics such as tumor size, presence of bilaterality, multifocality, Hashimoto's thyroiditis and tumor stage were not statistically significant, either. The evaluation of the response to treatment was finally performed in 64 patients from the ablated group and in 76 from the non-ablated group. An excellent response to treatment was observed in 81% of ablated patients *vs.* 87% of the non-ablated group, with a frequency of structural incomplete response of 1.6% and 1.4%, respectively; ($p = 0.9$). On the other hand, 17% and 12% of patients in each group had an indeterminate response. **Conclusion:** Low-risk ablated and non-ablated patients have a similar frequency of excellent initial and structural incomplete response to treatment. Long-term follow-up is needed to establish whether these initial responses are maintained over time, and thus further refine the indications of RA in this group of patients with DTC.

56715 DIFFERENTIATED THYROID CARCINOMA (DTC): PREABLATION THYROGLOBULIN AS A PROGNOSTIC MARKER OF INITIAL RESPONSE TO TREATMENT

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Introduction: Measurement of postoperative thyroglobulin levels just before radioiodine treatment, or preablation thyroglobulin (Preab Tg), has been proposed as a prognostic factor of persistence or recurrent disease. A Preab Tg below 10 ng/mL has been considered as a favourable predictive factor. **Objectives:** A) To evaluate postoperative Preab Tg levels under thyroid hormone withdrawal (THW) prior to remnant ablation in patients with differentiated thyroid carcinoma (DTC); B) to determine the initial response to treatment (IRT) and to analyse it in relation to Preab Tg; C) To define a cut-off level of Preab Tg predictive of IRT. **Methods:** Retrospective study. Between 2009 and June 2015, 84 patients underwent total thyroidectomy for thyroid cancer at our institution. 49 patients were excluded: 7 with no DTC, 22 without follow up, 3 without ablation, 16 with positive antithyroglobulin antibodies, and 1 because of ablation under recombinant human thyrotropin. Final population consisted of 35 patients. All underwent measurement of TSH (RV: 0.4-4 uUI/ml), TgAb (RV: < 40 UI/ml), and Tg (FS < 0.9 ng/mL) before ablation by chemiluminescence assay. IRT was defined as: Excellent (ER): undetectable suppressed and stimulated Tg (< 1 ng/ml), negative neck ultrasound (US) and no clinical evidence of disease; Acceptable (A): suppressed Tg < 1, but stimulated Tg between 1-10; Biochemical Incomplete (BI): persistently detectable Tg values with negative imaging studies and no clinical evidence of disease; and Structural Incomplete (SI): structural evidence of disease. **Results:** Of 35 patients included, 31 (88.5%) were women. Mean age: 43.7 ± 11.9 years. Initial risk of recurrence according to Argentine Intersocietary Consensus was very low in 3, low in 18, intermediate in 12 and high in 2 patients. Median Preab Tg was 13.25 ng/ml (range 0.46-252). IRT was classified as ER in 14 patients, A in 2, BI in 3 and SI in 9; in 7 patients data were missing. Preab Tg of patients with ER and A was significantly lower than those with BI and SI IRT ($P < 0.001$). Receiving operating characteristic (ROC) curve yielded a Preab Tg cut-off of 14.8 ng/mL with a sensitivity of 90% and a specificity of 89%. **Conclusion:** In our patients with DTC ablated under THW: 1) Preab Tg was an useful predictive factor of initial response to treatment; 2) A cut-off value of Preab Tg above 14.8 ng/ml was associated with persistence disease.

56636 DIFFERENTIATED THYROID CARCINOMA IN ACROMEGALY

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Introduction: Differentiated thyroid carcinoma (DTC) is the most frequent malignancy to be associated to acromegaly (A) but it is unknown if they have a different behavior. Pituitary tumors have 5% of cases a genetic or hereditary etiology. Germline mutations in the aryl-hydrocarbon receptor (AHR) interacting protein (AIP) account for the development of familial and more aggressive forms of A. **Objective:** To evaluate in A 1) DTC initial stratification, recurrence risk and response to therapy. 2) Germline mutations in AHR interacting protein (AIP). **Methods:** 7/59 (12%) A patients treated in our hospital were diagnosed with DTC, after routine thyroid ultrasound (TUS) and fine needle aspiration (FNA) in suspicious nodules. A was defined by IGF-1 levels greater than the upper limit of normal and OGTT-GH greater than 1 ng/mL. We considered TNM staging system and the risk of persistent/recurrent disease according ATA and LATS guidelines for DTC. Genomic DNA was prepared from blood samples. Six exons and the flanking intronic sequences of the AIP gene were amplified by PCR using specific primers. The amplification and sequencing of genomic DNA was realized for all the coding sequences gene. **Results:** We included seven A patients (p), age: 51 (R 31-63) years, 7 ♀, all with active disease in spite of different modality treatments. Diagnosis by FNA: Bethesda (B) V: 3p, B VI: 4p; DTC histology: 6 papillary, 1 follicular carcinoma were diagnosed metachronously in 5, and 2 synchronously. Follow up: 19-60 months. Associated neoplasms: 1 thyroid follicular adenoma, 1 Hürtlhe cell adenoma, 1 endometrial atypical hyperplasia, 1 colon polyp, 3 breast carcinomas. Surgery treatment: total thyroidectomy: 7p, lymphadenectomy: 2p; ^{131}I ablation: 4p. TNM stratification: I: 6p, III: 1p. Risk of recurrence LATS: very low risk: 5, low risk: 1 and intermediate: 1p; ATA: low risk: 6 and intermediate: 1p. Therapy outcome: Excellent response: 5p, biochemical and structural incomplete: 1p, 1p without follow up. 2 patient died because breast carcinoma, 5 alive. Germline mutation were performed in 5/7 p, all were negative, including the familiar acromegaly case , with intermediate risk, surgery reintervention for lymph node metastasis, and death not related to DTC. **Conclusions:** DTC in A patients have a good prognosis and didn't have an aggressive behavior when they are screened with TUS and FNA on suspicious nodules. Germline analysis didn't add more information in this group.

55900 DOES BETHESDA CATEGORY PREDICT AGGRESSIVE FEATURES IN THYROID CANCER?

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Introduction: Thyroid cancer (TC) is the most common endocrine malignancy and it usually presents as a thyroid nodule (TN). Fine needle aspiration (FNA) is the most accurate and cost-effective method for evaluating TN and it determines patient's follow-up. For example, when FNA shows malign or suspicious result it indicates surgery. Even though, FNA results are not considered during follow-up of a patient with TC. **Objective:** To analyze the relationship of FNA and TNM staging, risk of recurrence (RR), vascular invasion, extrathyroidal extension (ETE), incomplete tumor resection, lymph node metastasis and clinical outcomes. **Methods:** We evaluated 159 patients with diagnosis of differentiated thyroid carcinoma (DTC) attended between January/1999 and December/2016 at Hospital Universitário Presidente Dutra with pre-surgery FNA on their medical records and followed for at least 1 year. **Results:** 95% (n = 152) of the patients were female and 79.8% (n = 127) of all cases were papillary thyroid cancer (PTC). The average age was of 41.8 +/-13.62 years old. The most common FNA result was Bethesda II (28,9%; n = 46). Presence of ETE, vascular invasion and lymph node metastasis were more frequent when FNA was Bethesda V and VI ($p < 0,05$). There was no relationship between FNA and TNM staging, RR and incomplete tumor resection. 85% of patients evolved without evidence of disease. **Conclusions:** FNA results Bethesda V and VI were associated with some aggressive features of TC. So, FNA can have an impact on the follow up of patients with DTC. Future studies in a larger population are required to validate such an impact.

55070 DOES ELECTIVE IPSILATERAL CENTRAL NECK DISSECTION MODIFY ATA 2015-RSS AND TNM STAGING IN PAPILLARY THYROID CARCINOMA?

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Introduction: In patients with classic papillary thyroid carcinoma (PTC) with no clinical evidence of lymph node metastasis (cN0), elective central neck dissection (eCND) remains controversial. **Objective:** The aim of this study was to evaluate whether elective ipsilateral central neck dissection (eICND) along with total thyroidectomy bring further information that would modify previous staging in these patients, taking into consideration the incidence and the characteristics of the lymph node metastasis on histopathological exam. Also, we aim to assess possible pN1 risk factors, the incidence in post-operative complications and whether there is correlation between pN1 and change in the stages according to the Risk Stratification Score of the American Thyroid Association 2015 (ATA 2015 – RSS) and to the TNM Score. **Methods:** This is a prospective, observational study, involving 46 patients with cN0 PTC that underwent elective ipsilateral central neck dissection (eICND) along with total thyroidectomy. The number of metastatic lymph nodes, the biggest lymph node metastasis and the extra-nodal extension were assessed. **Results:** After elective dissection, 22 out of 46 patients (47.8%; IC 95%: 32.9%-63.1%) presented lymph node metastasis. Seventeen out of 45 (37.8%; IC 95%: 23.8%-53.5%) changed their ATA-2015 RSS initial risk staging. Ten out of 46 (21.7%; IC 95%: 10.49%-36.4%) were upgraded in TNM staging. Fourteen out of 17 reclassified patients had their ATA-2015 RSS initial staging changed due to lymph node metastasis bigger than 2 mm (mostly between 3 mm and 4 mm). General complication rate was of 8 in 46 (17.4%), of which 6 (13.04%) patients developed transient hypoparathyroidism, one patient (2%) developed permanent hypoparathyroidism and one patient (2%) had transient vocal cord paralysis. **Conclusion:** Elective dissection of levels VI ipsilateraly and VII has been shown to improve the initial recurrence risk (ATA 2015-RSS) and TNM staging in patients with PTC with no previous clinical evidence of lymph node metastasis. Further studies are necessary to evaluate the clinical impact of lymph node micro metastasis.

55195 DYNAMIC RISK ASSESSMENT IN PATIENTS WITH DIFFERENTIATED THYROID CANCER WITHOUT REMNANT ABLATION

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The therapeutic approach and the follow-up of patients with differentiated thyroid cancer (DTC) is currently individualized according to the risk of recurrence, with a lower tendency to perform remnant ablation (RA) in patients with a low risk of recurrence. While response to therapy assessment was validated for DTC patients treated with total thyroidectomy (TT) and RA, it has not been widely confirmed in patients treated with TT without RA. The aims of our study were to describe the characteristics of the population of patients treated with TT without RA, and to validate the response to therapy. We included 96 patients followed-up at least for 12 months after surgery. Considering the entire cohort, 85.4% were female and mean age was 47.5 years old. Based on the American Thyroid Association, 89.6% and 10.4% were classified as low risk and intermediate risk of recurrence, respectively. Patients had an initial excellent response to treatment in 57.3% of the cases, with a disease-free status at the end of follow-up of 74%. A minority of patients (1%) presented with an initial structural incomplete response, which was similar at the end of follow-up (1%). On the other hand, 41.7% of the patients had an initial indeterminate response, although only 22.9% remained with this response at the end of follow-up. Our data validate the responses to treatment in DTC patients treated with TT without RA as an effective tool for the dynamic risk stratification. Patients appropriately selected who did not receive RA have an excellent outcome, with a low frequency of structural incomplete response, even lower to that observed in low risk ablated patients.

56698 EFFECT OF RADIOIODINE THERAPY IN PATIENTS WITH THYROID MICROCARCINOMA

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Introduction: Thyroid microcarcinoma is defined as a tumor whose largest diameter is smaller than 1 cm. Several published guidelines consider such tumor as low risk neoplasia, raising a potential for changings in therapeutic protocols such as lobectomy instead of total thyroidectomy and no use of radioactive iodine ablative dose. **Objective:** To describe laboratory and scintigraphy findings of patients with thyroid microcarcinoma, who underwent standard treatment with total thyroidectomy and radioiodine ablation. **Materials and methods:** Description of the patients treated at our endocrinology service with a diagnosis of less than 1 cm differentiated thyroid carcinoma, submitted to total thyroidectomy and radioiodine therapy according to the service protocol. Patients were followed for 1 year after an ablative dose. We performed whole body scan (WBS), ultrasonography (USG) of the cervical region and measurements of serum thyroglobulin (Tg) and anti-thyroglobulin antibody (ATg) under stimulation of TSH as routine follow-up. **Results:** A total of 206 consecutive patients were followed between January 2010 and June 2016. In the WBS after ablative dose, we found 11 (5.3%) negative tests, 164 (79.7%) with cervical uptake (thyroid remnants) and 31 (15.0%) with images suggestive of residual cervical disease. Regarding Tg levels, 88 (42.7%) presented values < 2 ng/ml, 73 (35.4%) between 2 and 10 ng/ml and 33 (16%) were higher than 10 ng/ml. One year after the dose, we observed 176 (85.4%) patients with negative WBS, 26 (12.6%) with uptake in the cervical region and 4 (2%) patients with pulmonary field uptake. We verified a reduction in Tg values, with 81% of the patients reaching values < 2 ng/ml ($p < 0,01$), suggesting a beneficial effect of radioiodine. **Conclusion:** In patients with thyroid microcarcinoma we observed a high frequency of thyroid remnants in WBS, with Tg levels suggestive of residual disease. After radioiodine ablation, we observed significative reduction of Tg levels, suggesting a treatment benefit.

56709 ELEVATED TSH LEVELS IS ASSOCIATED WITH TUMOR SIZE IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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Introduction: Thyrotropin (TSH) is considered a proliferative factor in thyroid tissue. Some studies suggest the association of higher TSH levels with cancer, but there is conflicting evidence. **Objective:** To assess if there is association between TSH levels and DTC in patients with total thyroidectomy. Evaluate if TSH is related to tumor size in patients with DTC. **Methods:** Case control study including patients who underwent total thyroidectomy between 2006 and 2010. Individuals with DTC were considered cases and patients operated for benign multinodular goiter without DTC were defined as controls. We eluded other diagnoses such as Graves Basedow Disease. OR was calculated for the association between DTC and TSH over the normal level (> 4,5 mIU/L). We adjusted for age, gender and the presence of Hashimoto thyroiditis (HT) in histological sample using logistic regression. **Results:** 404 cases and 477 controls were included. 86.1% of the cases and 91.4% of the controls were female ($p = 0.013$). Mean age was 47.2 years in cases and 48.7 years in controls ($p = 0.12$). The histological type was papillary cancer in 86.9%. Mean TSH in cases was 2,55 and in controls 2,24 (mIU/L) ($p = 0,60$). A positive correlation between TSH levels and tumor size in patients with DTC were observed ($p < 0.001$). When dividing TSH in quartiles the first quartile of TSH average tumor size is 9.6 mm in the second and third quartile 13 mm and the highest quartile is 16.5 mm. There is a statistically significant difference between the first and last quartile of TSH ($p = 0.036$). We found an association between TSH over the upper limit and CDT with OR 2,64 (IC 95% 1.32-5.46) $p = 0,002$. In stratified analysis this association was observed for papillary cancer [OR 2,24 (IC 95% 1.14-4.44 $p = 0,01$], but not for follicular carcinoma. The association was present in absence of histological signs of HT with OR 7,1 (IC 95% 1,7-40). The adjusted OR was 2.34 (IC 95% 1,19-5,59, $p = 0,013$). There was no association between TSH and the presence of aggressive histology, multicentricity, capsule involvement, vascular invasion, perithyroidal soft tissues invasion or lymph node metastases. **Conclusion:** A significant association between elevated TSH and DTC was observed, using different cut levels of TSH. This association remains significant after adjusting for control variables.

56613 EVALUATION OF THE EFFECT OF SUPPRESSIVE DOSE OF LEVOTHYROXINE ON BONE MASS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH DIFFERENTIATED THYROID CARCINOMA

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Introduction: Levothyroxine (LT4) suppressive therapy (sLT4) is a cornerstone of treatment for children and adolescents with differentiated thyroid carcinoma (DTC). Nevertheless, the impact of supraphysiological doses of thyroid hormone in young patients before peak bone mass has been poorly studied. **Objective:** To evaluate the effect of TSH suppression on bone mass in a population of children, adolescents and young adults with DTC. **Methods:** Patients with diagnosis of DTC on long-term sT4 who initiated this therapy before 25 years of age were selected and compared to thyroidectomized patients under LT4 physiological replacement matched by sex, age and body mass index (BMI). The clinical variables were extracted from a Thyroid Outpatient Clinic cohort database. All patients were 19 years of age or older and underwent a dual-energy X-ray absorptiometry (DXA) to determine the bone mineral density (BMD) at lumbar and hip. **Results:** Thirty patients (96.6% papillary subtype, 76.7% females) under sLT4 therapy and 11 thyroidectomized individuals under LT4 replacement therapy (8 patients with medullary thyroid carcinoma and 3 with multinodular goiter; 72.7% of females) were included. There were no differences on age (27.8 ± 5.7 *vs.* 28.4 ± 7.1 years, P = 0.8), female/male ratio (8/3 *vs.* 8/3, P = 1.0) and BMI (24.0 ± 4.3 *vs.* 26.5 ± 3.4 kg/m², P = 0.1) between the groups. The dose of levothyroxine per kilogram (kg) of body weight was 2.4 ± 0.7 mcg/kg and 1.8 ± 0.3 mcg/kg in sLT4 and LT4 groups, respectively (P = 0.01). The median TSH was 0.20 (P25-P75 0.03-1.70) mUI/L in the sLT4 group and 2.90 (P25-P75 0.64-9.40) mUI/L in the patients on LT4 replacement therapy (P < 0.01). The median time for patients on sLT4 was 6.0 (P25-P75 3.0-9.5) years, while the other group had a median time of 6.0 (P25-P75 2.0-7.0) years on LT4 therapy. There were no differences in BMD in all the spots evaluated by DXA: lumbar spine (1.23 ± 0.17 g/cm² *vs.* 1.31 ± 0.14 g/cm²; P = 0.28), femoral neck (1.09 ± 0.13 g/cm² *vs.* 1.13 ± 0.17 g/cm², P = 0.52), and total femur (1.06 ± 0.15 g/cm² *vs.* 1.14 ± 0.16 g/cm², P = 0.28) for sLT4 and LT4 groups, respectively. All values were within the normal range, both in sLT4 treated and LT4 replacement therapy. Of note, no patient presented low BMD (Z-score < -2). **Conclusions:** Long term sLT4 therapy in young DTC patients are not associated with reduced BMD.

56603 EXPANDED EXOME ANALYSIS IN A FAMILY WITH NON-MEDULLARY THYROID CANCER CASES

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Introduction: Familial non-medullary thyroid cancer (FNMTC) corresponds to 3%-6% follicular thyroid epithelium carcinomas and is syndromic when patients present Mendelian tumor syndromes with low preponderance of thyroid tumors, such as Cowden's syndrome (CS), Gardner's syndrome, Carney's complex, and Werner's syndrome. Their clinical manifestations may vary between families. Gene mutations have already been associated with these syndromes and in 80%-85% of CS cases PTEN mutations have been identified. **Objective:** Investigate genetic alterations in a family with suspicious of syndromic FNMTC. **Methods:** The family from Piauí has 13 members diagnosed with thyroid, skin, breast, lung, gastric, oral or bone cancer. Although it does not clearly fit into any of the FNMTC syndromes, the possibility of being a CS was not ruled out. Therefore, PTEN gene (exon and promoter) mutations were first screened by Sanger's sequencing from peripheral blood DNA from a thyroid cancer patient. Subsequently, expanded whole exome sequencing (WES) of three cancer patients was carried out using the SureSelectXT Human All Exon V6 + UTR Capture Library kit (Agilent) and the Illumina® NextSeq™ 500 platform. WES generated 3.69-4.85 Gb of data/sample with coverage greater than 30x. **Results:** Six PTEN polymorphisms were detected. Bioniformatic analysis identified 5 SNVs with high potential to be mutations in the three patients and absent in databases and in 18 Brazilian individuals without cancer. Only one alteration seemed to segregate with the disease and was present in two asymptomatic individuals. However, it was discarded because the alteration located in X chromosome could not be inherited from the transmitting father with lung cancer to a male asymptomatic carrier. No indels were associated to the familial disease. Thus, it was ruled out the possibility of being a case of syndromic FNMTC, raising the hypothesis of being a case of familial cancer or family grouping, characterized by the lack of inheritance pattern, high number of individuals with sporadic tumors, presence of various types of tumors, age of onset like sporadic cases and that may result from similar environment and/or lifestyle. **Conclusion:** We conclude that this family could be classified as a familial case of non-hereditary cancer. However, studies of other regions of the genome or the use of alternatives pipelines would suggest a genetic predisposition to cancer.

56589 EXPANDED WHOLE-EXOME SEQUENCING IN A FAMILY WITH SUSPECTED NONMEDULLARY FAMILIAR THYROID CANCER

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Introduction: Approximately 90% of thyroid cancers originate from follicular cells are called non-medullary thyroid cancer (NMTC). Despite most of the cases are sporadic, familial or hereditary forms (FNMTC) represent 3%-6% of the cases. Several candidate chromosomal loci (TCO, fPTC/PRN, FTEN, NMTC1, MNG1, 6q22, 8q24) and genes of susceptibility (TERT, NKX2-1, SRGAP1, FOXE1 and HABP2) for FNMTC have been reported, but the genetic causes for FNMTC remain largely unknown. **Objectives:** To identify genetic alterations involved in the predisposition to the FNMTC of a Brazilian kindred through the Whole-Exome Sequencing (WES). **Methods:** The kindred had 3 patients with papillary thyroid cancer (PTC) and multinodular goiter (MNG) and 6 with MNG. Expanded WES was performed in the genomic DNA of two patients with PTC. Total DNA was isolated from peripheral blood samples and applied SureSelectXT Human All Exon V6+UTR Capture Library kit and Illumina NextSeq 500 for exon enrichment, capture and sequencing. Thereafter, a specific pipeline for the SNVs and Indels calls was applied. The single nucleotide variants (SNVs) and insertion/deletion (indels) selection criteria were: present in both sequenced patients, non-synonymous, located in exons and 3 and 5 UTRs, not present in the exome of 30 controls individuals, absent in databases and being damaging through SIFT, Polyphen2, Mutation Assessor, Mutation Taster, FATHMM programs. Interactions and involved pathways were analysed with STRING, GO, KEGG, DAVID databases. **Results:** No variants (SNVs, indels) in genes previously associated with FNMTC were found. In candidate chromosomal loci we identify a new exonic frameshift alteration in the MCM9 gene (locus 6q22) which is involved with cell cycle. Other members belonging to the MCM family have already been associated with sporadic papillary and anaplastic thyroid cancer. Three other new frameshift variants and 7 non-synonymous SNVs in different genes related to silencing, DNA replication, apoptosis, tRNA processing JAK-STAT and PI3K signaling pathway were identified. Two SNVs in CYTH2 and PIM1 genes were following investigated but did not segregate with the disease in this kindred. The other variants are being inquire in the family. **Conclusion:** Through WES analysis we have uncovered new alterations which could be potentially associated with FNMTC in this family however a complete validation in this kindred is needed.

56728 HISTOLOGICAL FEATURES OF MEDULLARY THYROID CARCINOMA RELATED TO PROGNOSIS

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Introduction: The influence of histological features in the prognosis and risk of recurrence has not been well established for medullary thyroid carcinoma (MTC) as it is for differentiated thyroid carcinoma (DTC). **Objectives:** To describe epidemiological, histological and clinical characteristics of MTC and analyze which parameters could influence the persistence of biochemical or structural disease. **Patients and methods:** Slides and paraffin blocks from 118 sporadic MTC patients or RET gene mutation carriers (multiple endocrine neoplasia type 2 – MEN2) who were submitted to thyroidectomy were revised by the team pathologist or data from original pathological reports were considered. Patients were followed prospectively in our MEN outpatient clinic. Outcome was based in the data available from calcitonin levels, neck ultrasound and imaging methods when necessary available until the last medical appointment. **Results:** A total of 118 patients, 75 sporadic (51 women) and 43 hereditary (23 women), mean age (range) of 49,3 (21-72) and 34 (7-73) years, respectively, were enrolled. Mean follow-up (range) was 87,6 (4,1-352,6) and 71,4 (1,1-199,5) months, respectively. In the MEN2 group, 26 patients from 9 families harbored mutation in codon 634, 16 patients from 7 families had ATA-MOD codon mutations (533, 609,768, 804,891 and M918V) and one patient had M918T mutation. They presented more CCH and multifocality and less distant metastasis at diagnosis ($p < 0,01$) and had less persistence of structural disease (13% *vs.* 32%) than sporadic patients. Both groups had similar rates of being free of disease (47%). Sporadic cases had more concomitant DTC (12% *vs.* 2%). Histological features significantly associated against being free of disease were: fusiform variant of MTC, thyroid capsule invasion, extra-thyroidal extension, vascular invasion, calcification, amyloid deposits, necrosis, multifocality and narrow or compromised surgical borders ($p < 0,05$). Major risk factors for having persistent structural disease were: thyroid capsular invasion, extra-thyroidal extension and vascular invasion. **Conclusion:** This study shows that histological features such as tumor necrosis, extra thyroidal extension and capsular invasion could be associated to worse prognosis in sporadic and familial MTC and suggests that they might be used to guide more aggressive initial treatment or closer surveillance in such patients.

56722 HORNER SYNDROME FOLLOWING A THYROID SURGERY – AN UNUSUAL COMPLICATION

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Case presentation: A 55-year-old woman with previous Hashimoto's thyroiditis diagnosis underwent total thyroidectomy with medial cervical lymphadenectomy for a highly suspect thyroid nodule on ultrasound (1.6 cm) that was previously investigated. The procedure underwent without intercurrences. Previous cytology exam demonstrated Bethesda VI pattern, showing several nuclear atypias and pseudoinclusions, suggesting papillary carcinoma with large poorly differentiated cells or medullary carcinoma. Serum calcitonin (< 2.0 pg/mL) and cervical ultrasound (without expansive mass or suspect lymph nodes) was performed previous to surgery. Histopathological examination revealed a papillary carcinoma with predominant Hurthle's cells of 15 x 15 x 6 mm with capsule and adipose tissue infiltration, without malignancy found in the 15 lymph nodes evaluated (T3N0). On postoperative day, a slight right-sided partial ptosis was noted. On ophthalmologic evaluation it was noticed that she also had myosis at that side, and after specific tests, Horner syndrome (HS) diagnose was made. However, facial anhydrosis and enophthalmos were not noted. The patient went home on the 2nd day feeling well with full levothyroxine replacement. Actually she is on the 3rd month of post-operative evaluation and a plastic surgery is proposed in the future. **Discussion:** HS is characterized by myosis, eyelid ptosis, enophthamos, anhydrosis and vascular dilatation of one half of the face resulting from damaged ipsilateral cervical sympathetic chain. HS is a rare manifestation of thyroid disease, usually associated with compression of the cervical plexus by the thyroid tissue. HS following thyroidectomy is an extremely rare complication, with few cases reported in the literature. Most cases presents as incomplete HS, not showing with anhydrosis and vascular dilatation. There are several theories to explain HS after thyroidectomy, including direct mechanical stress, indirectly via an injury of the anastomosis of various nerves and branches following the inferior thyroid artery, or by inflammation and hematoma of the area due to an excessive traction of the retractor. Once diagnosed, treatment remains mostly conservative and prognosis depends on the damage mechanism. **Final comments:** We report a case of Horner syndrome following a thyroid surgery that happened without complications. While HS appears to be a very rare complication of thyroid surgery, clinicians and surgeons should be aware of this potential complication.

56644 HORNER'S SYNDROME: A RARE POSTOPERATIVE COMPLICATION FOLLOWING TOTAL THYROIDECTOMY

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Case presentation: A 64-year-old woman developed unilateral miosis with partial ptosis and enophthalmia, associated with a pulsating cervical mass one week after total thyroidectomy for medullary thyroid carcinoma. A clinical diagnosis of Horner's syndrome was made. A postoperative CT scan did not show any structures compressing the sympathetic trunk, but a postoperative ultrasound showed an anatomical abnormality on the right common carotid. The patient was managed conservatively and presented no recovery after 1-year follow up. **Discussion:** Horner's syndrome (HS) is a very uncommon complication following total thyroidectomy, with an incidence of less than 0, 2% to 0, 3%. The exactly physiopathology remains unclear, but its development is presumed to complications during or after the surgical procedure such as direct mechanical stress or compression of the cervical sympathetic chain, anastomosis of the recurrent nerve, laryngeal superior nerve or sympathetic nervous branches around the inferior thyroid artery, formation of a hematoma compressing the cervical sympathetic chain, ischemia induced damage caused by a lateral ligature on the inferior thyroid artery trunk, and damage to the communication between the cervical sympathetic chain and the recurrent laryngeal nerve during its identification. After diagnosis, the management was conservative with few improvements observed. According to the literature, only 30% of the patients recover completely, mostly after 12 to 15 months. So far, there are no cases reported including an arterial malformation associated with the syndrome development. **Final conclusions:** This case report reveals an unusual postoperative complication related with the closeness anatomical relationship between the thyroid gland and cervical sympathetic trunk. Although rare, the importance of presenting this case is to alert surgeons about the possibility of an injury to the sympathetic chain after thyroidectomy, which may manifest as a pulsatile mass postoperatively secondary to a carotid abnormality.

56717 HYALINIZING TRABECULAR NEOPLASM OF THYROID: CASE REPORT

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Case presentation: A 71 years old woman presented to our department with a long-standing history of Hashimoto thyroiditis. Ultrasound showed a solid nodule, 2,7 x 1,8 x 2,1 cm, hypoechoic, with well-defined margins, without calcifications in the left lobe of the thyroid, with marked central vascularization. Three fine needle aspiration biopsy (FNAB) performed were nondiagnostic due to insufficient cellular material. The patient successfully underwent to total thyroidectomy and the microscopic findings were compatible with papillary thyroid carcinoma (PTC). Immunohistochemistry was positive to thyroglobulin, thyroid transcription factor 1 (TTF1) and showed MIB-1 (Ki-67) monoclonal antibody diffusely positive with membrane pattern. These findings were consistent with the diagnosis of hyalinizing trabecular tumor of thyroid (HTT). The patient is now on regular follow-up with no evidence of tumor recurrence or metastasis. **Discussion:** HTT of thyroid is a very rare neoplasm of follicular cell origin with a trabecular pattern of growth and marked intratrabecular hyalinization, which was first described as hyalinizing trabecular adenoma (HTA) in 1987 by Carney *et al.* Usually occurs between the 4th and the 7th decades of life, with a reported marked female predilection. The tumor may arise in a background of chronic lymphocytic thyroiditis, multinodular goiter, and it may also occur in association with PTC; and share some morphological and architectural similarities with paraganglioma and medullary thyroid carcinoma (MTC). Concerning the biologic and clinical behaviour, HTT should be considered as a benign neoplasm or a neoplasm of extremely low malignant potential, although rare cases of malignant HTT have been reported. Consequently, when this diagnosis is performed, clinical management should be conservative, which may include an annual follow-up in order to exclude the very rare possibility of recurrence. Radioiodine ablation is not standard and total or hemithyroidectomy can be considered as adequate treatments. **Final comments**: HTT of thyroid is unique and generally follow a benign clinical course. As rare cases of malignant HTT have been reported, it should be considered a neoplasm of extremely low malignant potential. Because of features that can mimic MTC and PTC, it is commonly misdiagnosed on FNAB cytology. Careful attention to cytologic features and a high index of suspicion can result in the correct diagnosis and guide clinicians to appropriate therapy.

55106 IMPACT OF HISTOPATHOLOGIC SAMPLE REVIEW ON THE RISK OF RECURRENCE AND RESPONSE TO THERAPY IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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Objective: To assess the change in the risk of recurrence (RR) and in the response to therapy in patients with differentiated thyroid cancer (DTC) after the review of the historic histopathologic samples (HPS) considering specific features proposed by the Modified Risk Stratification System from the ATA 2009. **Patients and methods:** Sixty-three available HPS from DTC patients with low and intermediate RR who underwent total thyroidectomy and remnant ablation in our hospital were reviewed. The RR and the response to therapy were re-assessed considering the new histological features (vascular invasion, extent of extrathyroidal extension, volume of lymph node metastases, presence of extranodal extension and status of the resection margins). **Results:** A change in the RR category was made in 16 of 63 cases (25,4%). Out of 46 patients initially classified as low RR, 2 of them were re-classified as intermediate RR, 4 patients as high RR and one as NIFTP. Out of 17 patients initially classified as intermediate RR, 3 were re-assigned to the low RR group, 5 as high RR and one as NIFTP. The percentages of structural incomplete response at final follow-up changed from 6.3 to 20% ($p = 0.53$) in patients with intermediate RR and from 2.2% to 0% ($p = 1$) in patients with low RR. **Discussion:** A detailed report of specific features in the HPS of patients with DTC gives a more accurate RR classification and estimation of the response to treatment, although it seems not to be absolutely necessary for predicting the final response to treatment.

56610 IMPACT OF SERUM TSH AND ANTI-THYROGLOBULIN ANTIBODY LEVELS ON LYMPH NODE FINE-NEEDLE ASPIRATION THYROGLOBULIN MEASUREMENTS IN DIFFERENTIATED THYROID CANCER PATIENTS

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Introduction: Differentiated thyroid cancer (DTC) is the most common endocrine cancer, accounting for 90% of the thyroid gland malignancies. DTC prevalence has risen in the last decades and, although the good prognosis expected for this tumor, recurrence in cervical lymph nodes (LN) occurs in up to 15% of patients after initial therapy. The diagnosis of cervical LN metastases of DTC is often complex and measurement of thyroglobulin in the washout of fine needle aspiration (FNA-Tg) has been used as an additional tool to detect LN disease. Nevertheless, the best cutoffs and influence of potential confounders are still a matter of debate. **Objective:** To evaluate the accuracy of FNA-Tg measurement to detect DTC metastases, seeking to assess the best cutoff point for the method, as well as to evaluate potential confounders, such as level of serum thyrotropin (TSH) and antithyroglobulin antibodies (TgAb). **Methods:** One hundred and thirty-eight patients with DTC and suspicious cervical LN were included. Patients underwent ultrasound (US) FNA guided aspiration, for both cytological examination and FNA-Tg measurements. Final diagnoses were determine by histological examination or by clinical and US follow-up for at least 1 year. **Results:** Between October 2012 and September 2015, 138 consecutive patients with DTC and suspicious cervical LN, detected by palpation or cervical US, attending the Endocrine Division at our Institution were invited to participate in the study. Data from 119 subjects (74.8% female; 45.9 years) were available for analysis. The median value of FNA-Tg in patients with metastatic LN (n = 65) was 3263.0 ng/mL (838.55-12507.5), while patients without LN metastasis (n = 54) showed levels of 0.2 ng/mL (0.2-0.2). According to the ROC curve analysis, the best FNA-Tg cutoff value to predict metastasis was 4.41 ng/mL, with sensitivity of 98% and specificity 96%. There were no differences in the median of FNA-Tg measurements between those on (TSH 0.16 mUI/mL) or off levothyroxine (TSH 99.41 mUI/mL) therapy (47.94 *vs.* 581.15 ng/mL, respectively; P = 0.79). Of note, the values of FNA-Tg in patients with LN metastasis (n = 65) did not differ between patients with positive or negative TgAb (88.8 ng/mL *vs.* 3263.0 ng/mL, respectively; P=0.57). **Conclusion:** Taken together our results demonstrated that measurement of FNA-Tg is an excellent tool for evaluation of suspicious LN in patients with DTC, independently of TSH status and presence of TgAb.

56601 IMPLEMENTATION OF THE BETHESDA SYSTEM IN FINE NEEDLE PUNCTURES (FNA) OF THYROID GLANDS WITH HISTOPATHOLOGIC FOLLOW-UP – EXPERIENCE OF PRIVATE HEALTH CENTER SANTIAGO DE CHILE

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Objective: To evaluate the Bethesda system by determining the concordance of the final histological diagnoses with reports of cytology by FNA of thyroid implanted with the Bethesda system in patients with thyroid nodules. **Materials and methods:** Retrospective, observational, descriptive study. The histology reports of the surgical (total or partial) thyroid resection of patients who consulted between the years 2014-2015 and who also had a FNA biopsy report were obtained from a database of the Pathology Service, to which it was applied Bethesda. **Results:** A review of the FNA report and surgical specimen histopathology was performed in 70 patients, 63 (90%) were women and 7 (10%) were men. The results of the FNA biopsies, according to frequency, were: Bethesda III (atypical indeterminate significance) with 34 patients (48%) constituting the most frequent diagnosis; Bethesda V, 12 Patients (17%), Bethesda IV, 10 patients (14%), Bethesda II with 7 patients (10%), Bethesda VI with 6 patients (9%) and Bethesda I, 1 Patient (2%). Of the histopathology results of the surgical biopsy, 41 (59%) were benign and 29 (41%) were malignant. Among the benign results, follicular hyperplasia was the most frequent and among malignant, papillary carcinoma. For the comparative analysis (FNA and surgical biopsy) we classified the patients into 4 groups: Group 1: Benign pathology (Bethesda 2): 5 (71%) were classified as benign and 2 (28% malignant). Group 2: Unsatisfactory study (Bethesda 1): 1 (100%) benign. Group 3: Undetermined study (Bethesda 3): 28 (82%) benign, 6 (17%) malignant. Group 4: Determines surgical behavior (Bethesda 4, 5 and 6): 21 (75%) malignant lesion and 7 (25%) benign lesion. **Discussion:** The application of the Bethesda system is very useful for making decisions, it is necessary to validate its utility in each institution. In this study benign lesions in definitive biopsies have a final frequency of 59% and malignant lesions of 41%. The group with the highest frequency was the Bethesda 3 group with a final correlation of 82% for benign and 17% for malignant, consistent with the results of other international studies.

56586 INTERIM BASELINE CHARACTERISTICS FROM RIFTOS MKI, A GLOBAL NON-INTERVENTIONAL STUDY ASSESSING THE USE OF MULTIKINASE INHIBITORS (MKIS) IN THE TREATMENT OF PATIENTS WITH ASYMPTOMATIC RADIOACTIVE IODINE-REFRACTORY DIFFERENTIATED THYROID CANCER (RAI-R DTC)

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Introduction: The RIFTOS MKI study was designed to compare the time to symptomatic progression from study entry in patients with RAI-R DTC for whom there was a decision to treat or not to treat with an MKI in the real-life setting. Here, we report interim baseline characteristics for the first 274 patients enrolled in the study. **Methods:** RIFTOS MKI is a non-interventional study enrolling patients with asymptomatic RAI-R DTC (NCT02303444). The decision to initiate MKIs at study entry was at the discretion of the treating physician. Final analysis will be performed once 700 patients have been enrolled and the last enrolled patient has been followed for 24 months. **Results:** Of 274 patients, the median duration of observation was 169.5 days. Patients have been enrolled from USA (n = 74), Japan (n = 55), Europe (n = 80), and rest of the world (ROW; n = 65); 54% were female and the median age was 68 years. Most patients had an ECOG performance status of 0 or 1 (97%) and distant metastases (81%). The most frequent histology was papillary (73%). The median time from initial diagnosis of DTC to study entry was 7 years. RAI refractoriness was mainly due to lack of RAI uptake (60%), primarily in Japan (80%). Japan had the shortest median time from RAI classification to initial visit (2 months) compared to USA (16.4 months), Europe (25.1 months) and ROW (4.3 months). The average dose per RAI treatment was also lower in Japanese patients at 3.4 GBq (91.9 mCi) compared with 5.5 GBq (148.6 mCi), 4.6 GBq (124.3 mCi), and 4.7 GBq (127.0 mCi) in patients from USA, Europe and ROW, respectively. Similarly, median cumulative activity of RAI was lower in Japanese patients (3.7 GBq; 100 mCi), compared with USA (7.8 GBq; 210.8 mCi), Europe (13.0 GBq; 351.4 mCi), and ROW (13.3 Gbq; 359.5 mCi). **Conclusions:** The RIFTOS MKI study is the largest non-interventional study in RAI-R DTC. The regional differences in treatment history observed in the RIFTOS MKI study reflect differences in accessibility and treatment practice. The study is ongoing.

56584 INVESTIGATION OF FOXE1 GENE EXPRESSION PATTERN AND THE INVOLVEMENT OF CPG ISLANDS PROMOTER METILATION IN PAPILLARY THYROID CARCINOMA

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Introduction: Forkhead box E1 (FOXE1) is a thyroid-specific transcription factor and has been associated with susceptibility to nonmedullary thyroid cancer. It was shown that hypermethylation of FOXE1 promoter lead to reduced expression in leukocytes and in different types of cancer (pancreas, skin, salivary gland). However the FOXE1 expression and its relation with the methylation pattern in thyroid cancer remains unclear. **Objectives:** To investigate FOXE1 expression in papillary thyroid tumors (PTC) and the involvement of CpG1 and CpG2 islands promoter methylation in its gene expression. **Methods:** FOXE1 expression was evaluated in 32 pairs of PTC tumor (T) and surrounding nontumor (NT) samples by RT-PCR. For *in vitro* studies FTC133, FTC236, FTC238, WRO and NPA cell lines were treated with 5-aza-2′ -deoxycytidine (5AZA) demethylating agent or DMSO (control). The methylation status of FOXE1 CpG 1 island (22 sites) and CpC 2 island (24 sites) was quantified by Bisulfite Sequencing. **Results:** In 75% of the patients FOXE1 expression was reduced in T when compared to NT samples ($p = 0.0116$) and this expression pattern was correlated with vascular invasion and lymph node metastases ($p < 0.05$). For the CpG 1 island the Bisulfite Sequencing of 8 tissue pairs showed that the T>NT methylation pattern occurred in only 37.5%, while all four samples on the CpG 2 island showed the T<NT methylation pattern ($p < 0.05$). After treatment with 5AZA there was up to increase in FOXE1 expression in the FTC133, FTC26, FTC28 and WRO cell lines cultures when compared to DMSO control ($p < 0.05$). However, the expression was similar in both NPA5AZA and NPADMSO. For the CpG 1 island the higher degree of methylation occurred only in FTC238 DMSO when compared to FTC28 5AZA ($p < 0.05$) while for the CpG 2 island it occurred in the FTC236, FTC238 and WRO DMSO cell lines as compare to 5AZA treated cells ($p < 0.05$). The NPA cell line showed no differences in the degree of methylation, as observed for CpG 1. **Conclusion:** These data shows that the expression of FOXE1 was reduced in PTC tumors as compared to nontumor samples and suggests that global hypermethilation of CpG 2 along with other regulatory mechanisms could be involved in the low FOXE1 expression.

56598 MEDULLARY THYROID CANCER: APPLYING A PREDICTING CANCER-SPECIFIC MORTALITY

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Introduction: Medullary thyroid cancer (MTC) is a rare neuroendocrine tumor derived from the thyroid parafollicular C cells that produce calcitonin. MTC occur both as sporadic tumor (75%) and as of mutations in proto-oncogene RET (25%) – Familial (FMTC) or multiple endocrine neoplasia (MEN) type 2. Despite low incidence, the death rate is high to thyroid cancer mortality in 10 years – 65%. The normograms are useful to predict some outcomes involved with multivariables. Recently, was made a nomogram for predicting cancer-specific mortality in MTC (CSM). **Objective:** To apply the CSM in a group of patients with MTC. **Methods:** Were analyzed in a retrospective study data from 9 patients charts (2 male and 7 females) with MTC in the thyroid cancer ambulatory. Were included: Age, gender, post operation serum calcitonin, vascular invasion, pathologic T status, pathologic N status, and M status. The data was put on CSM and with the punctuation we have a 10-year CSM for each patient. **Results:** The mean age in our group are 51,8 ± 13,4 years (median: 57 years – 19 to 63 years). The mean postoperative calcitonin levels were negative (< 2 pg /mL) for 02 female patients. The rest, had a mean postoperative calcitonin levels of 536 (median of 5,3-02 to 3765) pg /mL. No patient presented perivascular invasion. In TNM system, the results of T status for our patients were T1 (03%-33%); T2 (02%-22%); T3 (04%-45%), for N status were N0 (05%-55%); N1 (04%-45% – N1a – 02 e N1b – 02) and for M status were M0 (08%-89%); M1 (01%-11%). All patients were analysed with the multivariables included in CSM and 01 male that had a higher mortality in 10 years (35%) died 01 year after pos surgery, with distant metastases. A woman with a 10-year CSM of 04% died 08 years later to surgery, with an aggressive locoregional disease that was made two unsuccessful surgeries to control it. Another patient, with a postoperative calcitonin of 1017 pg/mL, still alive, but with nodular metastases in postoperative and with stable calcitonin levels for more than 10 years. **Conclusion:** Although MTC remains a challenging disease process to manage, the CSM, together with calcitonin serum levels doubling time, came as another resource to facilitate patient counseling in terms of prognosis and subsequent clinical follow up.

56694 MUCOEPIDERMOID CARCINOMA OF THE THYROID COMBINED WITH SQUAMOUS CELL CARCINOMA OF THE PALATE: A CASE REPORT

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Introduction: Mucoepidermoid carcinoma (MEC) is the most frequent malignant salivary gland tumor of the oral cavity. Its ethiopathogeny is unknown and clinically it may present with progressive symptomatic tumor growth. As a result of its diverse biological features, treatment and prognosis depend upon the histological grade, location and clinical stage of the tumor. Primary thyroid involvement is very rare, with only 33 cases described in the literature. **Case presentation:** A 63-year-old smoker woman presented with dysphagia and odynophagia for 5 months, associated with the emergence of ulcerated lesion in the hard palate and cervical lymphadenopathy. In March 2014, a biopsy revealed moderately differentiated squamous cell carcinoma (SCC). Within a month, the patient was submitted to maxillectomy with radical neck dissection on the right side and supraomohyoid neck dissection on the left side. During surgical procedure, nodal involvement and invasion of infrahyoid muscles and thyroid gland was observed. Histopathological analysis resulted in SCC of the palate with invasion of the maxilla, papillary thyroid carcinoma (PTC) on the left lobe and MEC on the right lobe, with supraclavicular node metastasis, confirmed by immunohistochemistry. A preventive tracheostomy was also performed, with evidence of several tracheal implants. Subsequent bronchoscopy showed multiple vegetative lesions in trachea and main bronchi. Biopsy revealed immature focal metaplasia. Later, the patient developed numerous subcutaneous nodules in the trunk and lower limbs, followed by oncological treatment and death. **Discussion:** MEC usually affects the salivary glands; however, it has been found in association with other glandular epithelia in head and neck region, such as the paranasal sinuses, nasopharynx, oropharynx, larynx, trachea and thyroid. It is a rare primary thyroid tumor, corresponding to 0.5% of malignant tumors of this gland. The histological grading is of utmost importance, since it correlates to the prognosis. **Final comments**: The presenting case is important due not only to the rarity of this neoplasia, but also to address its adverse developments, since MEC is typically considered a neoplasm of less aggressive behavior.

55821 NEK1, 5 AND 6 EXPRESSION CAN HELP IDENTIFY MALIGNANCY AND FOLLICULAR LESIONS IN THYROID NODULES

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The majority of thyroid nodules are benign; only 7%-15% are malignant. Nonetheless, the most important question to be answered for a patient with one or more thyroid nodules is whether they are malignant member nek family kinases have been identified as important regulators of cell cycle checkpoint, especially in the G2/M transition. Recent studies have shown that they can have crucial roles signaling pathways in DNA damage. These characteristics by the fact that the various members of the family are overexpressed in cancer make them interesting candidates targets in cancer diagnosis and therapy. In order to analyze the expression of NEK1, 5 and 6 as potential markers for diagnosis and prognosis for CDT, we used immunohistochemistry in 275 cases of thyroid nodules, including 162 papillary thyroid carcinomas (PTC) and 25 follicular thyroid carcinomas (FTC). 101 of the PTC cases were considered classic (CPTC); 13 were diagnosed as tall cell variants (TCPTC); and 48 variants follicular (CPVF). We also studied 73 benign lesions: 42 hyperplastic and 31 follicular adenomas (FA) and 15 normal tissues (NT). Cytoplasmic NEK1 expression distinguished malignant from benign thyroid nodules ($p < 0.0001$ with sensitivity = 94%, specificity = 47%, PPP = 81%, PPN = 74%) and cytoplasmic and nuclear NEK1 distinguished malignant from normal (cytoplasmic: $p < 0.0001$, sensitivity = 94%, specificity = 93%, PPP = 99%, PPN = 57%; nuclear: $p = 0.0030$, sensitivity = 55%, specificity = 86%, PPP = 98%, PPN = 15%). Cytoplasmic NEK1 expression was able to differentiate FVPTC from FA ($p = 0.0334$); FVPTC from hyperplasic ($p < 0.0001$); FC from hyperplasic ($p < 0.0001$); FA from hyperplasic ($p = 0.0018$). Nuclear NEK5 expression distinguished malignant from benign thyroid nodules ($p = 0.0144$, sensitivity = 27%, specificity = 50%, PPP = 58%, PPN = 20%) and FVPTC from hyperplasic ($p = 0.006$). Finally nuclear NEK6 expression differentiate only malignant from benign thyroid nodules ($p = 0.0035$, sensitivity = 20%, specificity = 57%, PPP = 50%, PPN = 25%). Expression nuclear NEK1 protein was associated with clinical or pathological characteristics of the aggressiveness, being more expressed in patients with multifocality ($p = 0.0272$) and without thyroiditis ($p = 0.0102$). While NEK6 had an increase in expression in patients without metastasis, Nek6 cytoplasmic ($p = 0.0292$) and nuclear Nek6 ($p = 0.0015$). Our data suggest that the expression of NEK1, 5 and 6 may help in the differential diagnosis of malignancy, and NEK1 and 5 diagnosis of thyroid follicular lesions.

56668 PAPILLARY THYROID CARCINOMA MIMICKING SUBACUTE THYROIDITIS: CASE REPORT

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Subacute thyroiditis is characterized by self-limited cervical pain, an increase of the thyroid volume and alteration of thyroid hormones (thyrotoxicosis can occur in up to half of the patients). The etiology is not fully understood, but it might be associated with a viral condition. It's five times more common in women. US typical features include enlargement of the thyroid, focal hypoechoic zones or diffuse hypoechogenicity, and in some cases lymphadenopathy. These findings usually accompany hard and tender thyroid gland. On the other hand, thyroid cancer usually presents itself as a non-painful solitary nodule or mass. Here we describe a patient with papillary thyroid carcinoma (PTC) whose clinical presentation was highly suggestive of thyroiditis. **Case:** A.R.R.P., 28 years old, female transgender seek the Emergency Room for acute pain in the cervical region with dyspnea and dysphagia. The patient had goiter's history and notices a significant increase in recent weeks. In the initial evaluation, he presented with an enlarged cervical mass, extremely tender to palpation. The clinical picture was suggestive of a subacute thyroiditis and thyroid function tests, VSG and imaging exams were requested. Thyroid and VSG test showed no abnormalities (TSH 1.44 mUI/ml and free T4 1.0 ng/dl and VSG of 19 mm). Imaging exams were performed. The ultrasonography (US) showed a heterogeneous lesion with 7.5 cm with liquid areas, suggestive of goiter. The fine needle aspiration (FNA) biopsy showed Bethesda 3 classification. Due to patient's complaint of dyspnea, the patient underwent TC which displayed a lesion of 7.9 x 7.5 x 6.4 cm that diverts the trachea. Owing to compressive symptoms, the patient underwent thyroidectomy. Surprisingly, the final anatomopathological exam revealed classical PTC (6.5 x 6.0 x 4.5 cm) with metastasis in 23/35 lymph nodes examined. The tumor was classified as T3N1bMx and the patient received radioactive iodine 131 100 mci. One year after she was submitted to a new lymphadenectomy after a diagnosis of cervical relapse. Nowadays the patient is considered as a complete biochemical response. Thyroid carcinoma mimicking subacute thyroiditis has been rarely reported in the literature. The present case highlights the importance of been aware of this atypical presentation, which is missed by the initial US. In conclusion, atypical PTC presentation should be considered in the differential diagnosis of subacute thyroiditis.

56617 PREOPERATIVE DETECTION OF TERT C228T AND BRAFV600E MUTATIONS: RELATIONSHIP WITH CLINICOPATHOLOGIC FEATURES IN PAPILLARY THYROID CARCINOMA

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Introduction: Only few studies preoperatively analyzed TERT promoter mutations in differentiated thyroid cancer (DTC) patients, and all suggested that the knowledge of the TERT mutation status might help to guide the extent of initial surgery. Interestingly, a significant co-occurrence of TERTC228T with BRAFV600E mutations has been reported and proposed as a fingerprint of more aggressive behavior. **Objective:** We analyzed the prevalence of TERT promoter mutations in papillary thyroid carcinoma (PTC) tumors and examined their relationship with clinicopathologic features and positivity for BRAF-V600E mutation. **Methods:** 59 consecutive patients with high risk thyroid nodules after US evaluation requiring FNA examination, were selected from January to April 2014 and had confirmed histological diagnosis of PTC. Subsequently, eight patients were excluded due PCR failure and 6 for insufficient clinicopathologic data. The BRAF T1799A was detected by PCR – restriction fragment length polymorphism (RFLP) and standard PCR was performed for direct genomic DNA sequencing to identify TERT promoter mutations. **Results:** The prevalence of TERT promoter mutation C228T was 8,9% (two cases of oncocytic variant, one of classical PTC and one of trabecular PTC), which was slightly lower than previously reported prevalence in FNA samples. The BRAFV600E mutation was found in a frequency of 66.7% (30/45), which was slightly higher than the generally observed prevalence. All four cases of TERT promoter positive PTCs additionally harbored BRAFV600E mutations. 4/11 cases classified as stage III-IV were double (BRAF and TERT) mutated. C228T TERT mutation was associated with more advanced age ($p = 0.02$) and AJCC stage ($p = 0.03$). **Conclusion:** Preoperative determination of BRAFV600E and TERT promoter mutation status can be performed on cytologic preparation using lavage fluids collected from needle rinsing. A low prevalence of concomitant BRAFV600E/TERT mutation was found and showed correlation with age and disease stage. The preoperative knowledge of BRAFV600E/TERT combined mutation status might be useful as prognostication and for planning individualized treatment and follow-up.

56699 PREVALENCE OF CENTRAL LYMPH NODE METASTASIS IN PAPILLARY THYROID CANCER PATIENTS WITH SUSPICIOUS AND UNCERTAIN SONOGRAPHIC PATTERNS IN THE PREOPERATIVE STAGING ULTRASOUND

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Introduction: Preoperative staging ultrasound (US) in papillary thyroid carcinoma (PTC) is the key tool for identifying possible central lymph node metastasis (CM). However, the accuracy of different sonographic patterns for predicting the presence of clinically relevant central lymph node metastases (CRCM) is still uncertain. Furthermore, when thyroiditis is present, it is not clear whether group VI uncertain lymph nodes (usually attributed to thyroiditis) are associated to CRCM. **Objectives:** To establish the prevalence of CRCM in CPT patients with abnormal central lymph nodes (Cc) on US that underwent CLNs resection. Secondarily, to assess the prevalence of CRCM in uncertain CLNs on US, either in the presence or absence of thyroiditis. **Methods:** We performed a retrospective review of all PTC patients who were staged by expert radiologists in thyroid cancer and underwent a CLNs resection in our institution between 2013 and 2016. CLNs on US were informed using three categories: Normal, Uncertain and Suspicious. The number and size of every CLNs was evaluated in each case, as well as the presence or absence of thyroiditis in the US, and correlated with their pathologic report. CRCM were defined as more than 5 metastatic CLNs (any size) or any metastasis larger than 2 mm. **Results:** We reviewed 161 patients, 74% were women and the mean age at diagnosis was 39 years. CM were present in 67% (108/161), 56% being CRCM (91/161). CLNs were informed as suspicious in 48% (78/161) and 83% of them (65/78) had CRCM. CLNs were informed as uncertain in 52% (83/161) and 30% of them (25/83) had CRCM. Amongst them, 12% (10/83) correspond to CRCM between 2-5 mm and 18% (15/83) to CRCM between 5-10 mm. Prevalence of CRCM was 26% (22/51) in patients with thyroiditis and uncertain CLNs on US and 40% (10/25) in patients without thyroiditis and uncertain CLNs on US, which was not statistically significant ($p= 0,5$). **Conclusions:** As expected, patients with suspicious CLNs pattern in US had high prevalence of CRCM. A third of patients with uncertain CLNs on US presented CRCM. Even though they were small volume CM (2-10 mm), a non-negligible 18% were between 5-10 mm. When thyroiditis is present on US, 25% of patients with uncertain CLNs, that could have been interpreted as reactive CLNs, had CRCM. This should be taken in consideration in the decision whether to perform or not central lymph node resection in this subgroup of patients.

55766 PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL IN RADIOACTIVE IODINE-REFRACTORY PULMONARY METASTASES OF DIFFERENTIATED THYROID CARCINOMA

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Introduction: Distant metastases (mainly lungs) are a rare situation in patients with differentiated thyroid cancer (DTC). Two thirds of these patients will become refractory to radioiodine therapy (RAI) and when progression occurs, they will be amenable for treatment with multikinase inhibitors (MKIs). It is important to identify the time of structural progression to decide when is the best moment to start with this treatment. **Objectives:** To define the time of progression free survival (PFS) and the overall survival (OS) in RAI refractory pulmonary metastases. **Methods:** We analyzed 610 files of patients with DTC, 9.8% (n = 60) had pulmonary metastases. Thirty-one patients were included in the analysis, after exclusion of those with diffuse RAI uptake, aggressive histology and those who were rendered disease free after RAI. Progressive disease was defined as an increase of at least 30% in pulmonary lesions bigger than 1 cm or identification of new lesion/s. The time of progression was divided in: fast (< 1 year), moderate (1 a 5 years) or slow (> 5 years). **Results:** The median OS was 15 years since DTC diagnosis and 5 years since the development of distant metastases. The median time of PFS was 3.75 years. Time of progression was moderate in 59%, fast in 23.5% and slow in 17.5%; 71% of the patients progressed at the end of follow-up. Shorter PFS was associated with age older than 45 years (P = 0.005), metastases larger than 1 cm (P = 0.03) or in multiple sites (P = 0.01) and follicular histology (P = 0.01). **Conclusion:** RAI-refractory pulmonary metastases usually progresses in 3 to 5 years after initial therapy. This will probably be the moment to start therapy with a MKI.

56721 RADIOIODINE INDICATIONS IN DIFFERENTIATED THYROID CANCER IN A REFERENCE UNIVERSITY HOSPITAL COMPARED WITH THE 2015 AMERICAN THYROID ASSOCIATION (ATA) GUIDELINES

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Introduction: The aim of Iodine-131 (RI) post-surgical ablation of the gland remnant in differentiated thyroid cancer (DTC) is to facilitate the early detection of recurrence based on serum thyroglobulin levels (Tg) measurement and subsequent systemic screening with radioiodine. In addition, it allows treating eventual foci of micro or macroscopic disease. In the past, it was conventionally indicated in the vast majority of patients with DTC; currently, the selection based on individual recurrence risk has been introduced. The ATA published in 2015 intending to provide adequate post-thyroidectomy RI indications. Main goal: It was to assess the concordance between RI activities administered in a period of 3 months contrasting with 2015 ATA guidelines in a University Hospital. **Methods:** A retrospective study was carried out reviewing the records of 67 patients who received RI consecutively between December 2016 and February 2017 in our center, who is a reference for several specialists from various hospitals and regions of the country. Patients were stratified according to ATA criteria at risk levels considering clinical data, tumor biopsy, Tg, thyroid ultrasound. Data was compared with medical indication of RI activity. **Results:** A total of 67 patients were evaluated; 22 of them were excluded from the study. Of the 45 patients analyzed, 91% were women, with a mean age of 42.5 years. According to clinical, biopsy and Tg levels patients were divided into 3 groups of risk, in blind form, without be aware of the administered RI dose. The 62% of the patients were at high risk (89% females), 11% at intermediate risk (all females) and 27% at low risk (92% females). The mean therapeutic activity received was as follows: A) high risk: 121 mCi, 50% received the dose suggested by the ATA (under 75 years: 150-200 mCi); B) intermediate risk: 86 mCi (only 20% of patients received the recommended dose for remnant ablation b corresponding to 30 mCi); C) low risk: 79 mCi (12 patients in the 3 months period, which according to ATA would have no indication). **Conclusion:** The adherence to the ATA 2015 Guidelines in our media was lower than expected, a discrepancy that may be due to slow implementation by referrals. The current mode of risk stratification suggested by these guidelines implies a careful analysis based on a good pathological report, and reliable cervical ultrasound and TG measurements. On the other hand, it should be considered that ATA guidelines evidence based data are still relatively controverted.

55899 SKIN METASTASIS AS AN INITIAL PRESENTATION OF FOLLICULAR THYROID CARCINOMA: A CASE REPORT

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Case report: 25 year-old male presented 5 years ago violaceous lesions in right lateral cervical region that spread, after 3 months, to the chest wall. He underwent an excisional biopsy of a neck lesion whose anatomopathological and immunohistochemical results confirmed little differentiated folicular thyroid carcinoma (FTC). After that, he was submitted to total thyroidectomy with bilateral lymph node dissection that confirmed FTC with lymph node metastasis (T2N1bM1). Then, the patient was subjected to two doses of 200 mCi of 131 radioiodine (RAI) and the post dose scanning showed uptake in the cervical region, lungs and chest wall. However, there was no reduction on lesions or fall of thyroglobulin levels after the doses. So, patient was considered to have a RAI-refractory disease. Due to growth of lung lesions, patient began therapy with kinase inhibitor therapy (sorafenibe). During treatment, there was reduction of skin lesions but the medication had to be stopped after 3 months because of hand-foot syndrome grade IV. Subsequently, new sorafenib cycle with lower doses was attempted but again patient had hand-foot syndrome. He is currently under TSH suppressive therapy with levothyroxine and awaits for levantinib. **Discussion:** Skin metastases of thyroid cancer (TC) usually develop in patients with advanced disease. In rare cases, they appear as the initial manifestation in individuals with no previous history of TC. These lesions have purplish color and present as nodules, papules or plaques and may bleed because they are very vascular. The most common location is the skull but it can also appear on the neck, face, chest and abdominal wall or the surgical scar. The skin metastasis are generally accompanied by metastasis in other places and indicate poor prognosis. Isolated skin metastases are rare. The approach of these lesions is not well defined but tyrosine kinase inhibitors seem to be a therapeutic option. **Final comments**: Skin Metastases are rare, usually accompanied by metastases in other sites and sign advanced disease. However, there are cases of indolent disease. Optimal approach of these injuries need to be established and these patients should be closely followed because of the risk of complications and progression of these lesions.

56661 THYROID CARCINOMA PRESENTING WITH PARANEOPLASTIC LEUKOCYTOSIS

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Paraneoplastic hematologic syndromes are rarely symptomatic and herald a poor clinical outcome in a variety of cancers. These conditions are usually detected after cancer diagnosis associated with advanced disease. They rarely require specific therapy, and may improve with successful treatment of the underlying malignancy. Here we firstly describe a metastatic poorly differentiated thyroid carcinoma associated with severe leukocytosis. A 37-year-old female patient was referred with a three-month history of cough and cervical enlargement. At physical examination, she presented 6 cm anterior cervical mass at right thyroid lobe. Fine needle aspiration biopsy of thyroid nodule had been performed and diagnosed follicular neoplasia, Bethesda IV. CT scan imaging showed a 6.0 x 3.5 cm right thyroid nodule, displacing her trachea, extensive bilateral cervical lymphadenomegaly (levels II to V) and multiple bilateral pulmonary nodules, up to 7.0 cm, indicative of metastatic disease. Laboratory evaluation revealed a marked increase in white blood cell count 68,000/mcL, mainly eosinophils. Infection disease, bone marrow infiltration and primary haematological disease in the absence of atypias in peripheral blood smear were discarded. Cervical lymph node excisional biopsy diagnosed metastatic poorly differentiated thyroid carcinoma with solid-trabecular pattern. Despite the metastatic disease, serum thyroglobulin was barely increased, 262 ng/mL, and thyroid function was normal. The extensive pulmonary disease demanded urgent therapy and systemic chemotherapy with cisplatin and doxorubicin was firstly prescribed. After the first cycle, total leukocytes declined to 18,000/mcL with no more eosinophilic prevalence. Nevertheless, just before the second chemotherapy cycle, her leukocytes had already increased to more than 80,000/mcL, suggesting poor prognostic disease. Paraneoplastic leukocytosis rarely occurs in thyroid tumors, mainly described in anaplastic thyroid carcinoma. Leukocytosis resulted from abnormal production of hematopoietic cytokines by tumor cells or secondary to the inflammatory reaction. We alert for this unusual presentation of thyroid carcinoma, as paraneoplastic leukocytosis is a very rare condition and undifferentiation must be the underlying disease condition.

55923 UNUSUAL METASTASES FROM DIFFERENTIATED THYROID CANCER

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Introduction: Complications related to metastatic disease are the main cause of specific mortality in patients with differentiated thyroid cancer (DTC). The most common sites of metastases are lungs and bones. Other localizations are infrequent and they have been reported as isolated cases or small series. The impact of these unusual metastases (UM) in patient management and prognosis remains largely unknown. **Objectives:** to evaluate the prevalence of UM in DTC patients, to define their clinicopathological characteristics and to analyze its relevance in DTC management and mortality. **Patients and methods:** We retrospectively reviewed the file records from 7 databases. UM were diagnosed by: a) biopsy and/or b) radioiodine uptake + elevated thyroglobulin (Tg) levels and/or c) uptake of 18-FDG in the PET-CT scan + elevated Tg levels. We analyzed histopathologic characteristics, clinical presentation, localization, time of diagnosis (synchronic *vs.* metachronic presentation), diagnostic and therapeutic modalities and final outcome of patients. **Results:** UM were diagnosed in 29 out of 2,986 DTC patients (1%). The most common site of UM was the central nervous system (CNS, 31%); the second was skin (20%), followed by liver and non-cervicomediastinal lymph node (8% each). 21% of the patients had more than one UM. In 93% of the cases, UM coexisted with either lung and/or bone metastases and/or locoregional disease. Papillary histology was found in 75% of cases; 79% were metachronic with DTC diagnosis, and 76% fulfilled radioiodine refractoriness criteria. Half of the patients reported symptoms related to the UM. In 76% of the cases, therapeutic decisions were influenced by the diagnosis of the UM. Median follow-up after the diagnosis of UM was 16 months; 16 patients (55%) died due to DTC related causes, with a mean survival of 8.5 months. The most frequent cause of death was CNS metastasis progression. **Conclusions:** UM are a rare entity in patients with DTC. They are usually metachronic and radioiodine refractory. UM were found in patients with widespread disease, and treatment strategies were modified by their diagnosis. UM were associated with poor prognosis and disease specific mortality.

56604 USEFULNESS OF POST-THERAPY WHOLE-BODY SCAN IN PATIENTS WITH LOW-RISK DIFFERENTIATED THYROID CANCER

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Introduction: Radioactive iodine (RAI) is widely used in the management of differentiated thyroid cancer (DTC). When RAI is indicated, current guidelines indicate a post-therapy whole-body scan (WBS) in order to document iodine's avidity of structural disease, and to update disease stage. However, the utility of the post-therapy WBS for low-risk DTC has been questioned. **Objective:** Evaluate the diagnostic value of post-therapy WBS in the population of low-risk DTC. **Material and methods:** From a cohort of 1045 DTC patients consecutively attended in Thyroid Outpatient Clinic of the Endocrine Division of Hospital de Clínicas de Porto Alegre we selected those who have undergone RAI, performed post-therapy WBS and were classified as low-risk according to the 2009 ATA risk system. Persistent disease was defined as the presence of clinical or radiological and/or biochemical disease (thyroglobulin under suppression > 1 ng/mL and/or stimulated thyroglobulin > 2 ng/mL). **Results:** A total of 295 low-risk DTC patients were studied. The age at diagnosis was 46 ± 14 years, 260 (88%) women, with a tumor of 1.8 cm (P25-P75 1.0-3.0) and 218 (74%) with TNM AJCC stage I disease. The post-operatory stimulated-Tg was 5.1 ng/dL (P25-P75 1.3-13.5) and the RAI activity 94 ± 30 mCi. Post-therapy WBS showed no distant metastasis in all studied patients (n= 0/295). At a 6 year (P25-P75 3-9) follow up, 192 (81%) patients were disease free, 36 (15%) had persistent biochemical disease and 10 (3%) structural disease, 5 (1.5%) of which had distant metastases not detected on the post-therapy WBS. **Conclusion:** In low-risk DTC patients, post-therapy WBS do not contribute to risk stratification nor to long term prognosis. Performing the post-therapy WBS in the low-risk population seems unnecessary, and avoiding this procedure could reduce the number of hospital visits and treatment costs.

THYROID HORMONE ACTION

56585 INVOLVEMENT OF TRIIODOTHYRONINE (T3) ON AMPHIREGULIN (AREG) ONCOGENE THROUGH EXTRANUCLEAR PATHWAYS IN A BREAST ADENOCARCINOMA CELL LINE (MCF-7)

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Introduction: Data from the literature suggests that triiodothyronine (T3) has a role in the development of breast cancer (BC), through the modulation of the expression of particular genes via classical nuclear, and non-classical extranuclear pathways. Several works led to the discovery of amphiregulin (AREG), a protein member of the epidermal growth factor (EGF) family that positively modulates the epidermal growth factor receptor (EGFR). When expressed, AREG induces mammary epithelium proliferation; thus, AREG is classified as an oncogene, with its expression related to several cancer types. However, the relationship between AREG expression and the presence of thyroid hormones remains largely unknown. **Objective:** To elucidate the modes of action of T3, aiming at verifying AREG protein synthesis in the breast adenocarcinoma cell line MCF-7, using specific drugs to block intracellular signaling pathways. **Methods:** MCF-7 adenocarcinoma cell lines were subjected to treatment with 10-8M T3 for 1h, alone or combined with either the PI3K inhibitor LY294002 (LY), the ERK/MAPK inhibitor PD98059 (PD), or the integrin αvβ3 inhibitor RGD peptide (RGD), which were added to the medium 1h before T3. AREG protein synthesis was assayed using western blotting. All experiments were repeated at three different moments for all treatments and times, between the second and third passage, in triplicate. For statistical analysis, we used ANOVA complemented with Tukey test and a minimum 5% significance was adopted. **Results:** Our results show that T3 (for the group LY 2,2 ± 0,4; PD 1,7 ± 0,1 and RGD 3,1 ± 0,1) significantly elevated AREG gene expression levels related to the control group (1 ± 0,1 for all treatments). Nonetheless, when associated with a pathway inhibitor (T3 + LY 1.0 ± 0.2); (T3 + PD 1.4 ± 0.1) and (T3 + RGD 1.6 ± 0.1), there was a significant downregulation of AREG expression, when compared to the T3 group. **Conclusions:** In this study, we demonstrate that T3 increases AREG gene expression through extranuclear pathways. The data obtained present a great potential for application, since the identification of new signaling pathways and other mechanisms by which thyroid hormones act can lead to the development of specific drugs, to activate or block such pathways, promoting desirable effects and blocking undesirable ones.

56576 SIRT1 EXPRESSION REGULATION BY THYROID HORMONES AND RESVERATROL IN THE HEART AND PRIMARY CARDIOMYOCYTES CULTURE

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Sirtuin 1 (SIRT1) is a NAD+-dependent deacetylase, which protein expression is upregulated in hypothyroidism and downregulated in hyperthyroidism, conditions associated with decreased and increased heart mass. SIRT1 activation by the polyphenol resveratrol (RESV) attenuates cardiac hypertrophy of pathologic models. We aim to evaluate RESV effect in non-pathologic cardiac hyperthrophy induced by thyroid hormone (TH) and whether it is a direct effect on cardiomyocytes. Adult mice received daily T3 injections (50 ug/100g BW) for 14 days. RESV (50 mg/100g BW) was administered by gavage to euthyroid and hyperthyroid mice (EU+R and HYPER+R) during 14 days, simultaneously to hormone injections. Morphometry was analyzed by eosin-and-hematoxylin-stained ventricular histological sections. Primary cardiomyocytes cultures derived from neonates rats were exposed to T3 (10-8M) and/or RESV 50 µM during 24h. Protein content was investigated by western blotting and mRNA, by real time PCR. Statistical analysis: One-way ANOVA, post-test Student-Newman-Keuls (*$p < 0.05$, n = 6-8 mice/group and n = 4 cultures with replicates). HYPER presented 1,4-fold increase in heart mass and an increase of 13% in left and right ventricles (LV and RV) walls thickness, and 1,7-fold higher expression of hypertrophy marker ANF, together with decreased protein expression of SIRT1 and PPARa (37% and 43%, respectively). HYPER+R exhibited 1,7-fold increase in protein expression of SIRT1, but not PPARa, and did not attenuate T3-induced heart hypertrophy. SIRT1 mRNA expression did not change, but HYPER presented 1,6-fold and 1,9-fold increase in mRNA expression of MHCa and PGC1a, respectively, and RESV in euthyroid group augmented 2-times PGC1a mRNA. In cardiomyocytes cultures, T3 alone and RESV alone increased 3-times SIRT1 protein expression and PPARa content did not change. RESV increased 2-times SIRT1 RNA expression with or without T3, however T3 alone did not alter SIRT1 RNA. T3 and RESV, alone or together, induced 1,4-fold increase in PGC1a mRNA expression. Thus, RESV chronic administration to mice could not avoid the development of hyperthyroid- induced heart hypertrophy. Acute exposition of T3 and RESV to cardiomyocyte cells induced a different effect from *in vivo* studies on the protein and mRNA expression of the evaluated genes, suggesting specific mechanisms occurring in the *in vivo* and *in vitro* context, which are under investigation.

56198 SUPRAPHYSIOLOGICAL TRIIODOTHYRONINE (T3) DOSE OR AFTER PI3K PATHWAY INHIBITION UP-REGULATION ADIPONECTIN EXPRESSION IN ADIPOCYTES

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Introduction: Triiodothyronine (T3) has a direct impact on the proliferation and differentiation of adipocytes. Adiponectin is an adipokine, products from the adipose tissue (AT), with important metabolic effects. The interaction between T3 and adiponectin concentration remains largely unclear. **Objectives:** Examine the effects of T3 on the modulation of adiponectin expression, and the involvement of the phosphatidyl inositol 3 kinase (PI3K) signaling pathway in adipocytes. **Methods:** We treated 3T3-L1 adipocytes with supraphysiological (SII = 1000 nM) T3 dose during one hour, in the absence or the presence of the PI3K inhibitor LY294002; the group treated with the inhibitor alone was named LY and untreated is control (C). RT--qPCR and Western blotting were used for mRNA and protein expression analyses. **Results:** T3 increased adiponectin mRNA expression in SII (2.87 ± 0.11, $p < 0.001$), compared to the C (1 ± 0.22). This increase in adiponectin mRNA in SII was not affected by LY294002 (3.55 ± 0.48, $p > 0.05$). Interestingly, the inhibition of the PI3K pathway increased adiponectin levels (7.2 ± 0.24, $p < 0.001$) independent of T3, compared to the C group. Western blotting confirmed these results on the effects of T3 to SII group on adiponectin protein expression. However, PI3K inhibition had an effect on adiponectin protein levels that where elevated by supraphysiological T3 doses: LY294002 inhibited the T3-mediated effects on adiponectin levels, indicating a role of the PI3K pathway in the translation of adiponectin. In order to confirm the inhibition of the PI3K pathway by LY294002, we evaluated p-Akt protein expression, which was decreased in the LY group (0.57 ± 0.01, $p < 0.01$) and increased by T3 in the SII (2.67 ± 0.13, $p < 0.001$), compared to C (1.00 ± 0.12). The used the cycloheximide (CHX) was use to examine directly or indirectly action by T3, completely inhibited the effects of T3 on adiponectin mRNA expression (0.69 ± 0.09, $p < 0.001$) in presence the CHX. **Conclusion:** T3 increased adiponectin and p-AKT expression. In the presence of LY294002, the stimulatory effects of T3 on p-AKT and adiponectin expression were eliminated; that effect was more pronounced at the protein level of adiponectin. These results suggest that if the PI3K pathway is inhibited, the T3-dependent stimulation of adiponectin expression is downregulated; this is highly clinically relevant when those inhibitors are used for treating diseases, such as cancer and obesity.

56634 THE DECREASE IN HIF-1A PROTEIN SYNTHESIS BY TRIIODOTHYRONINE (T3) OCCURS WITHOUT PARTICIPATION OF THE EXTRANUCLEAR PATHWAYS ERK/MAPK AND INTEGRIN AVB3 IN BREAST ADENOCARCINOMA CELL LINES (MCF-7)

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A myriad of environmental risk factors, pathological conditions and physiological agents, such as thyroid hormones (TH), have been proposed to influence the development of breast cancer (BC). Triiodothyronine (T3) has been shown to increase adenocarcinoma cancer cell proliferation *in vitro*. In the literature it has been demonstrated that high levels of HIF-1a expression in human breast cancer are related to mammary carcinogenesis and molecular modifications resulting from the process of tumor vascularization. This is seen in high-grade ductal carcinoma in situ which has high levels of HIF-1a. However, it is largely unknown whether, and by which mechanism, T3 affects HIF-1a protein synthesis. **Objective:** To elucidate the modes of action of T3 its ways of action HIF-1a protein synthesis in the breast adenocarcinoma cell line MCF-7, using specific drugs to block intracellular signaling pathways. **Methods:** MCF-7 breast adenocarcinoma cells were subjected to treatment with 10-8M T3 for 1h, alone or combined with the ERK/MAPK inhibitors PD98059 (PD) and the integrin αvβ3 inhibitor RGD peptide (RGD). Appropriate control groups were employed. HIF-1a protein synthesis was assayed by western blot. Statistical analysis was performed by ANOVA for completely random model, complemented with Tukey test for multiple comparisons, regarding a 5% significance level. **Results:** Our results show that HIF-1a protein synthesis is significantly decreased in the presence of T3 (PD 0.73 ± 0.03 e RGD 0.83 ± 0.05) as compared to the control group (C) under treatment with PD98059 (1 ± 0.08) and RGD (1 ± 0.09); the same occurs when comparing group C *versus* ERK/MAPK inhibitor (0,70 ± 0,02). A significant increase in HIF-1a expression was observed in the presence of RGD (1,35 ± 0,05) compared to group C. Comparing T3 alone to T3 plus PD98059 or RGD, no significant difference was observed, as well as between PD98059 alone and PD98059 combined with T3 (0.79 ± 0.01. Comparing RGD with (0.85 ± 0.04) and without T3, a significantly lower HIF-1a expression was observed. **Conclusions:** Founded on these results, it was concluded that the protein synthesis of HIF-1a it dependent of T3 action and does not occur through ERK/MAPK and integrin αVβ3 extranuclear pathways. These data obtained present a great potential of application, once the identification of thyroid hormones involvement can provide the development of specific drugs to avoid resistance and promote best prognosis on adenocarcinoma breast human cancers.

56724 TRIIODOTHYRONINE (T3) ASSOCIATED WITH ESTROGEN (E2) SHOWS PROTECTIVE EFFECTS IN HUMAN OSTEOBLASTOS

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Introduction: T3 is known to increase osteoblast and osteoclast activities *in vivo* and *in vitro*, however little is known about its effects on the transcription of target genes, such as the bone remodeling stimulators RANKL and OPG. Like T3, estrogen is also important for bone metabolism regulation. Nonetheless, the effect of the combined action of these hormones, regarding conditions mimicking hipothyroid, euthyroid, and hiperthyroid states associated with hypoestrogenic state or normal E2 levels, on these genes are scarce in literature. **Objectives:** To evaluate T3 action on RANKL and OPG gene expression and the modulatory action of E2 on T3 effects, in human osteoblast cultures. **Methods:** Mesenchymal stem cells (MSCs) were obtained by enzyme dissociation from adipose tissue from female patients who underwent abdominoplasty. MSCs were submitted to osteogenic differentiation for a 16-day period, in DMEM medium and addition of osteoinductive agents. After cell characterization, the obtained osteoblasts were treated for 72 hours, with either of the following T3 doses: Infraphysiological – T3I (10-10M), Physiological – T3F (10-9M) and Supraphysiological – T3S (10-8M), with or without E2 – Infraphysiological – E2I (10-9M) and Physiological – E2F (10-8M) – doses. Gene and protein expressions were assessed by RT-qPCR and Western Blotting, respectively. For statistical analysis, ANOVA was used, followed by Tukey post-test at a 5% significance level. **Results:** All T3 concentrations raised RANKL gene expression, and only T3F treatment increased OPG mRNA level. In association with E2, there was a suppression of RANKL expression, and OPG upregulation in the T3S group, while T3I and T3F groups showed an increase in RANKL and OPG expression. **Conclusion:** Mimicking hyperthyroidism does not alter OPG expression, although it induces RANKL expression. When both hormones are associated, estrogen can increase OPG expression, and also reduce the increased RANKL level. There is a clear protective action by E2, as its expression raised OPG levels with all T3 doses.

56612 ANALYSIS OF THE AMERICAN THYROID ASSOCIATION (ATA 2015) AND AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGIST (AACE 2016) GUIDELINES REGARDING THE MANAGEMENT OF THYROID NODULES - WHAT HAS CHANGED?

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Introduction: Thyroid nodule is defined as a lesion that distinct from the rest of the thyroid parenchyma through ultrasonography (US) or other sensitive imaging methods. Its prevalence on inspection and palpation varies between 3% and 7% and for the US without suspicion it varies between 19% and 76%. It occurs more often in older women, iodine deficient areas, and in patients with a history of radiation exposure. The clinical importance of understanding this condition lies in the need to exclude the possibility of cancer ranging from 7% to 15% of cases. Two recent important guidelines establish recommendations regarding the management of thyroid nodules, differing in few but relevant aspects. **Objective:** To compare the last two consensus of thyroid nodules. **Methods:** The authors reviewed the latest guidelines published in the literature of the thyroid nodule. **Results:** The indication of fine-needle aspiration (FNA), the surgical decision based on cytology and the risk factors for thyroid carcinoma remained the same in relation to previous consensus of these societies. **Conclusions:** The new guidelines emphasizes the superiority of the sonographic characteristics of the nodule for a better therapeutic decision. Volume comparison, besides the characteristics, is the most relevant aspect. Finally, we observed the Doppler devaluation for therapeutic decision.

THYROID NODULE

56727 ANALYSIS OF THYROID NODULES SUBMITTED TO FINE NEEDLE ASPIRATION IN ARACAJU, BRAZIL

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Introduction: Thyroid nodules are common findings in medical practice and represent the main manifestation of thyroid diseases. Most nodules present with benign ultrasonographic characteristics. Nodules that present with malignant ultrasonographic findings should be submitted to fine needle aspiration. Our study aimed to compare ultrasonographic findings with the cytopathological results from fine needle aspiration biopsy (FNAB) and develop the epidemiological profile of the sampled population. **Methods:** Prospective and descriptive clinical study with quantitative analysis. The results of ultrasound examinations and FNAB were taken from 238 patients, randomly sampled from November (2016) to March (2017) in a private setting. The patients joined the study after agreeing with the Informed Consent Form. The study was approved by the National Ethics and Research Committee with human beings. The numerical variables were tested for normality using the Shapiro-Wilk test, normal distribution values will be presented as mean and standard deviation, categorical variables will be described by their absolute and relative frequencies, analysis using GraphPad Prism 7. **Results:** From 238 patients, 221 were female and 16 male, with a mean age of 50.4 years (sDEV 15.03; SEM 0.97). One hundred and one (43.3%) had a positive family history of thyroid disease, 30 (12.9%) of the patients had a positive family history of thyroid cancer and 152 (65.5%) had previously undergone FNAB. Heterogeneous parenchyma was observed in 16 patients, while non-heterogeneous parenchyma was observed in 218 cases. 202 (87%) presented 1 nodule, 22 (9.4%) presented 2 nodules and 6 presented 3 nodules. Of the nodules, 66 had a solid texture, 11 had a cystic texture and 158 had a mixed texture. The Bethesda classification, 93 were Thy-1, 134 were Thy-2, 5 were Thy-3a and 4 were Thy-5. **Conclusion:** A higher prevalence of thyroid nodules was observed in the female population, in adults and in patients with a positive family history of thyroid disease, corroborating previous studies. The studied sample presented a higher amount of single nodules and non-heterogeneous parenchyma, with a predominance of mixed texture and absence of calcifications. The peripheral vascularization was the most evident and the Bethesda Thy-2 classification was the most prevalent.

56723 APPLICATION OF THE BETHESDA CLASSIFICATION FOR INDETERMINATE THYROID NODULES

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Introduction: The introduction of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), in 2007, allowed establishing a uniform six-tiered reporting system for thyroid fine needle aspiration (FNA). The TBSRTC kept from the former system the non-diagnostic, benign and malignant categories and divide the indeterminate for malignancy (called gray zone) into the three diagnostic categories: Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS; III); Follicular Neoplasm/Suspicious for a follicular neoplasm (FN/SFN; IV) and Suspicious for malignancy (SM; V). Each of the diagnostic categories carries an estimated risk of malignancy and a usual management suggestion according to the literature available and has contributed significantly to the standardization of cytological diagnostic of thyroid nodules. **Objectives:** The study aimed to evaluate the influence of TBSRTC in surgery decision of patients included in categories III, IV and V as well as the rate of malignancy. **Methods:** The study is a retrospective, transversal and observational analysis. Data were collected from the medical records of the patients who performed FNA from 2002 to 2007 with an indeterminate cytological report and compared to the medical record data of the patients who performed FNA from 2010 to 2015 with a cytological report in categories III, IV and V of TBSRTC. After the data collection, the groups were compared to regarding surgical incidence and rate of malignancy. **Results:** Among the 1460 patients who underwent FNA in the period from 2002 to 2007, 153 patients (10.4%) had an undetermined cytological report. Of these patients, 85 had total or partial thyroidectomy (55.5%) with benign result in 58 patients (68.2%) and malignant in 27 patients (31.8%). However, in the period from 2010 to 2015, 88 out of 921 patients (9.5%) had a cytological report in categories III, IV and V of TBSRTC. In the same period from 2010 to 2015, 40 patients underwent total or partial thyroidectomy (45.5%) with 18 benign results (45%) and 22 malignant results (55%). **Conclusion:** When comparing groups of patients with undetermined cytology thyroid nodules that were classified before and after TBSRTC, it was shown that most patients classified before TBSRTC underwent unnecessary surgery (thyroidectomy) with 68.2% benign results *versus* 45% on the group classified after TBSRTC.

55828 CLINICAL, LABORATORY AND ULTRASOUND PROFILE OF PATIENTS WITH THYROID CYSTS

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Introduction: Thyroid nodules are very frequent in the general population, affecting about 6% of adult women and 2% of men. An accurate ultrasonographic evaluation shows that approximately two thirds of all women and one third of all men have small nodules in their glands. True simple thyroid cysts originating from benign epithelial cells are rare. Most cystic nodules are partially solid structures with cystic degeneration (mixed or complex nodules). The clinical-laboratory characteristics of solid or complex thyroid nodules are well known because of their possible association with malignancy, but the characteristics of simple cystic nodules have not been fully determined. **Material and methods:** The study was conducted on 225 patients with thyroid nodules ((18 men and 207 women) ranging in age from 18 to 87 years who were divided into 4 groups: Group 1 – patients with simple cysts; Group 2 – patients with simple cysts associated with solid nodules; Group 3 – patients with pure solid nodules; and Group 4 – patients with complex nodules. TSH, free T4, free T3, thyroglobulin, anti-thyroperoxidase antibody, anti-thyroglobulin antibody and anti-TSH receptor antibody (TRAB) were determined. **Results and discussion:** Simple cysts were not infrequent in the population studied. Single simple cysts occurred in a younger population compared to the remaining types of nodules. Single simple cysts were less frequent than simple cysts associated with solid nodules. single simple cysts, cysts associated with solid nodules and complex cysts were found to be all benign in the present study. **Conclusion:** Complex cysts were the most frequent nodules and also the largest among these patients. Anti-TPO, anti-Tg and thyroglobulin levels were higher in patients with simple cysts associated with Clinical Hypothyroidism and Hashimoto Thyroiditis. The single case of thyroid carcinoma was detected here in a single Solid Nodule. Acknowledgment to the Endocrinology Leage of Unaerp years 2015 and 2016 and to Unaerp for the support.

56571 CLINICAL, ULTRASONOGRAPHIC AND CYTOLOGICAL CORRELATION OF THYROID NODULES IN HOSPITAL DE CLINICAS IN URUGUAY

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Introduction: Thyroid nodules (TN) are common in general population. Their assessment is important to rule out malignancy (5%-15%).Thyroid ultrasonography (US) is the imaging technique with the highest sensibility to recognize and characterize thyroid lesions. Neither feature is enough to differentiate between benignity and malignity, but at least 2 features together increase malignity rate.US-guided aspiration biopsy of thyroid lesions (FNA) is the most accurate, profitable and safe method in the thyroid nodules research. **Objective:** The aim of this study is to analyze clinical, ultrasonographic and cytologic features of TN and to assess sensibility of each one on correlation with malignity presence. **Methods:** Observational, prospective, transversal and analytic study. We studied 276 patients, who assist to an endocrinologic polyclinic in university hospital between June 2010 and December 2014, of whom 237 patients had TN and underwent a FNA. **Results:** Of the 237 patients, mean age were 56.89 ± 0.86 ys and 93% were female. 2.5% had head and neck radiation background and 5.5% had thyroid carcinoma family background. 10.5% had locorregional symptoms, 59.5% were euthyroid and 36.3% were thyroid peroxidase antibodies positive.US features: 56.4% had solid-cystic nodules, 43.3% central vascularization, 33.7% hypoechoic nodules, 12.8% microcalcifications and 2.1% adenopathies. Citology: 81.9% were benign, 3% follicular lesion or atypia, 6.3% follicular or Hürthle neoplasm, 2.1% suspicious for malignancy, 4.2% malignant and 2.5% were non diagnostic. Correlation between US features and cytology suspicious for malignancy were significance for adenopathies ($p = 0{,}005$), size < 1 cm and > 4 cm (p 0.027), as well as relation between microcalcifications and hypoechogenicity ($p = 0.037$) or central vascularization ($p = 0.032$). Histopathologic diagnostic of 28 operated patients showed 17 carcinomas, of those 9 were malignant, 4 suspicious for malignancy and 4 Hürthle neoplasm on FNA. 1 patient had malignant cytology and histopathology showed Hashimoto's thyroiditis. **Conclusions:** Malignancy prevalence in our work was 7.2%. Suspicious US features by themselves are not enough to differentiate between benignity and malignity, however, association between patterns sonographically suspicious had a high correlation with Bethesda category IV, V and VI on FNA. Hence cytology is a cornerstone on TN assessment. **Keywords:** Thyroid nodule, fine needle aspiration biopsy of the thyroid, cytology, thyroid Doppler ultrasonography

56726 ECTOPIC THYROID TISSUE CONCOMITANT TO BENIGN NODULES IN TOPIC THYROID

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Case presentation: W.A.P., male, 67 years old, in postoperative colon adenocarcinoma follow-up, performed a follow-up thoracic CT scan whose result was a mass in the anterior mediastinum. The biopsy of the mediastinal lesion evidenced a fragment of ectopic thyroid tissue without atypia. Scintigraphy investigation evidenced a hipercapping ectopic tissue. Doppler ultrasound (US) showed heterogeneous thyroid at the expense of four nodular images with ultrasound characteristics suggestive of benignity. A whole-body I-131 scan showed topical thyroid with preserved uptake of the radiopharmaceutical and focal area of hypercaption of the tracer in the anterior mediastinum. The patient was asymptomatic and euthyroid, being followed up with US thyroid, due to the benign characteristics of the nodules and laboratorial thyroid function. **Discussion:** Ectopic thyroid tissue (ETT) is any thyroid tissue located outside its normal topography. The most commonly found ETT is located at the base of the tongue; lingual thyroid accounting for 90% of reported cases. The mediastinal localization is rare, around 1% of cases. It has been suggested that an excessive migration of thyroglossal duct remainder is the cause of ETT in mediastinum. Thus, most of the described cases are not true development abnormalities, but just intrathoracic extensions of a thyroid with habitual location. In the present case, there was no tomographic or scintigraphy evidence of link between ETT and the topic thyroic, which lead us to believe it is not an intra-thoracic extension. However, diagnostic certainty would be possible only through the surgical approach. Scintigraphy is important for the differential diagnoses with other mediastinal masses, as well as to exclude other sites of ectopic tissue. Fine needle aspiration may be useful in the presence of nodular ectopic gland or when coexisting with ortotopical thyroid it may raise suspicion of metastasis from thyroid cancer. However, definitive diagnosis is only possible with excision of the ectopic tissue. Because an ETT is associated with a low malignant potential, some authors opt for surveillance; a compression of the mediastinal structures implies surgical treatment. **Final comments**: Although mediastine ETT is a rare localization, it should be remembered as a differential diagnosis of mediastinal masses. In this sense, it is important to know the methods of complementary diagnosis and how to manage this abnormality.

56679 INDETERMINATE THYROID NODULES ON CYTOLOGY: ULTRASOUND, CYTOLOGICAL SUB-CATEGORIZATION AND CLINIC-LABORATORY FEATURES RELATED TO MALIGNANCY RISK

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Introduction: Indeterminate cytology remains the main challenge in thyroid nodules (TNs) investigation. **Objective:** To evaluate the ultrasound (US), cytological sub-categorization and clinic-laboratory features of TNs with indeterminate cytology, according to malignancy risk. **Methods:** TNs showing Bethesda III (BIII) or IV (BIV) cytology were included and classified according to its US patterns applying TIRADS score. Benign outcome was considered when one of the following findings occurred: histopathology, hyper functioning nodule at scintigraphy, a second FNAB showing benign cytology or a significant reduction of nodule volume (> 50%) in follow-up. Malignant outcome was confirmed by histopathology. Clinical characteristics and serum TSH/FT4 were assessed. Four cytological sub-groups were created: 1) only architectural disarrangement (AUS-A); 2) only nuclear atypia (AUS-N); 3) architectural disarrangement with nuclear atypia (AUS-A/N) and 4) suspect oncocytic pattern (AUS-O). AUS-A was defined by cell crowding and/or micro follicle formations and the considered AUS-N were: enlarged and elongated nucleus, irregular contours, grooves, pseudo inclusions and chromatin clearing. **Results:** 100 TNs classified as BIII (36% malignant) and 41 as BIV (42% malignant) were included. The majority (30.8%) of TNs were classified as low suspicion (TIRADS 4a), 29% as moderate risk (TIRADS 4b) and 4,1% as highly suggestive of malignancy (TIRADS 5), while 36% were classified as TIRADS 3 (probably benign). The frequency of malignancy increased according to TIRADS classification (18%, 25.6%, 62.8% and 100% in TIRADS 3, 4a, 4b and 5). AUS-A pattern was the main determinant for malignancy in TIRADS 3, since isolated AUS-N pattern was not related to malignancy in any case of this group. TSH was higher, but not significant, in malignant TNs (2.5 x 1.9 mIU/L; p = 0.11). **Conclusions:** In BIII and BIV TNs the US pattern might help to distinguish benign from malignant lesions in a subgroup of patients. In TIRADS 5 lesions, the high risk for malignancy justifies thyroidectomy. In TIRADS 3, the cytological sub-categorization may give additional help in this discrimination, since the absence of AUS-A was an important finding related to benignity. Serum TSH tended to be higher in patients with malignant TNs. Finally, there are still uncertainties in TIRADS 4a and 4b and probably more urgency in defining additional diagnostic tools are needed, like molecular analysis for example.

56718 INTRA-THYROID NON-FUNCTIONING PARATHYROID CARCINOMA MISDIAGNOSED AS FOLLICULAR NEOPLASM IN A PATIENT WITH THYROID NODULES

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Case: A 45-year-old woman underwent fine needle aspiration biopsy of a suspect thyroid nodule on isthmus-measuring 15 mm in the largest dimension. The nodule was moderately hypoechoic and with a non-ovoid shape. The cytopathology showed follicular cells with enlarged, round, irregular, dark chromatin nucleos, focal grooves, in large irregular sheets with cell crowding and microfollicles, gross fibrous cores with arborescent pattern similar to papillae was also found, leading to the final diagnosis of a Bethesda IV. Other hypoechoic thyroid nodule in the left lobe measuring 42 mm in the largest dimension was also investigated showing Bethesda III diagnosis with architectural disarrangement and some low-grade atypias. Pre-operative evaluation showed normal thyroid function and calcemia. After total thyroidectomy the patient developed transient hypoparathyroidism and on histopathological examination, a coalescent mass measuring 6 x 5 cm was found in the left lobe and isthmus composed by cells of monomorphic pattern with bland nuclear atypia, in acinar pattern, with nodules permeated by coarse fibrosis bands, angioinvasion and focal invasion of surrounding fat, diagnosed as parathyroid carcinoma. Immunohistochemistry was negative for thyroglobulin, TTF-1, synaptophysin and positive for chromogranin and cytokeratin. **Discussion:** We describe a patient with a suspect thyroid nodule and cytological appearance of thyroid neoplasia, but histopathological revealing a parathyroid carcinoma. Surprising the calcemia was normal previously to surgery, suggesting a non-functioning disease. Parathyroid carcinoma is a rare disease that usually presents with severe primary hyperparathyroidism. Less than 10% of cases are non-functioning, making the diagnosis more challenging, especially when it presents as an intrathyroid nodule. Fine-needle aspiration may cause misdiagnosis since it is described significant overlap between cytological features of parathyroid and thyroid lesions. Concerning the gross papillary pattern described in cytology it might be explained by delicate fibrous beams that permeate this neoplasia misdiagnosed as suspect of papillary thyroid carcinoma. **Conclusion:** This case highlights the importance to include as differential diagnosis of suspected thyroid lesions, parathyroid origin, because of their morphological similarities. To our knowledge this is the first report of a nonfunctioning parathyroid carcinoma presenting as an intrathyroidal nodule misdiagnosed previously as a thyroid carcinoma.

56731 PERCUTANEOUS ETHANOL INJECTION ON CYSTIC THYROID NODULES

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Objective: To evaluate the efficacy and safety of percutaneous ethanol injection (PEI) in reducing the volume of cystic thyroid nodules. **Materials and methods:** From May 2015 to November 2016, a total of 13 patients (female: 11, age: 59.6 ± 10.7 years) with benign cystic thyroid nodules undergone PEI with ethanol 96° and volume variation was followed using thyroid ultrasound. **Results:** The mean baseline volume of 11.53 ± 3.17 cm^3 reduced to 1.16 ± 0.72 (volume reduction: 89% ± 0.06, $p < 0.01$) of the initial volume. Number of sessions was 4.5 ± 2.2 per patient. The mean follow-up was 4.6 ± 3.1 months. The most frequent side effect was transient and self-limited pain. **Conclusions:** PEI is effective and safety in reducing the volume of cystic thyroid nodules in the short term follow-up.

56624 RISK OF MALIGNANCY IN THYROID NODULES BETHESDA III: SUBCATEGORIES AUS AND FLUS

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Bethesda category III (B III) classification of thyroid fine-needle aspirates (FNAs) estimates a risk of malignancy of 5%-15%, however recent studies suggest higher malignancy rates up to 37%. Subcategories atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS) may also differ in terms of risk of malignancy, with the former showing a higher rate. **Objectives:** To determine risk of malignancy in B III FNAs; to evaluate clinical, laboratory and cytological features predictive of malignancy and to assess differences between subcategories AUS/FLUS. **Methods:** Retrospective study of 1500 satisfactory FNAs performed between 2011 and 2016. Demographic characteristics, thyroid function tests, antithyroid peroxidase antibodies (TPOAb) positivity and nodule size were recorded from all patients. BIII FNAs were subclassified as AUS or FLUS according to Bethesda (B) criteria. Follow up data for FNA repetitions (FNAr) or surgery were obtained. **Results:** 39 (2.6%) FNAs were classified as BIII; 29 (74.4%) FLUS and 10 (25.6%) AUS. Median age: 54 years (range 22-76; 87% were females. Thyroid function tests showed euthyroidism in 60.5% and hypothyroidism in 36.8% of cases. TPOAb were positive in 28%. Median nodule size was 21 mm and median follow up was 24 months. Excluding patients without follow up, overall malignancy rate was 6.9%: 1 papillary thyroid carcinoma (PTC) and 1 thyroid lymphoma (TL). Risk of malignancy was higher in AUS *vs.* FLUS (33% *vs.* 0% respectively, p = 0.005). Clinical, laboratory data and nodule size were not predictors of malignancy. 8 patients (20.5%) underwent surgery; histologic diagnosis was benign in 7 and PTC in 1. 51% of patients underwent FNAr: only 2 had a second suspicious cytology, with a final diagnosis of TL and follicular adenoma. Of patients without FNAr or surgery, no one showed clinical or ultrasound changes. TPOAb positivity was more frequently found in AUS than FLUS (60% *vs.* 20% respectively, p = 0.02). No other differences were found between subcategories. **Conclusions:** in this population, rate of B III FNAs and risk of malignancy are similar to those originally estimated by B. FLUS subcategory was predominant; however AUS conferred a significantly higher risk of malignancy. AUS subcategory had a higher rate of TPOAb positivity. Estimation of malignancy rate in B III FNAs may be better predicted by classification in cytological subcategories.

56615 ROL DE LA ECOGRAFÍA LARÍNGEA TRANSCUTÁNEA EN LA EVALUACIÓN PERIOPERATÓRIA DEL PACIENTE CON CANCER DE TIROIDES

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Objetivo de aprendizaje: Analizar el rol de la ecografía transcutánea de laringe en la evaluación pre y post-quirúrgica de los pacientes sometidos a tiroidectomía. **Revisión del tema:** La laringoscopía directa usando un nasolaringoscopio flexible es considerada el *gold standard* en la evaluación de la movilidad de las cuerdas vocales. Pero, la ecografía laríngea transcutánea en la actualidad es una alternativa no invasiva, muy válida en la evaluación perioperatoria. El examen laringoscópico prequirúrgico en los pacientes con cáncer de tiroides a los cuales se les realiza tiroidectomía total debe efectuarse rutinariamente para detectar parálisis de cuerdas vocales, alteración que se encuentra en el 2% de los pacientes y en el 50%-67% de los casos son asintomáticas. La parálisis recurrencial prequirúrgica puede vincularse a la extensión local de la enfermedad, por lo que su reconocimiento permite planificar la cirugía inicial y el eventual tratamiento adyuvante posterior de manera más adecuada. En el post-operatorio el examen es un indicador de calidad, al poner en evidencia las parálisis de cuerdas vocales resultantes de la lesión del nervio laríngeo recurrente durante la tiroidectomía. Hallazgos en imágenes. La extensión del movimiento de las cuerdas vocales se establece en grados: grado I: movimiento completo o simétrico de ambas cuerdas vocales; II: movimiento disminuido o impar en una o ambas cuerdas vocales; III: sin movimientos en una o ambas cuerdas vocales. Detalles del procedimiento. El paciente se examina en decúbito dorsal con el cuello extendido. El transductor se coloca de manera axial sobre la porción media del cartílago tiroides y se examina la laringe de manera cráneo-caudal hasta visualizar tanto las cuerdas vocales verdaderas como las falsas. Durante la evaluación se examina la movilidad de las cuerdas indicando al paciente que pronuncie las letras see –cart. También se emplea el Doppler pulsado en la porción vibrante de la cuerda vocal y Doppler espectral para evaluar velocidad de desplazamiento de la cuerda vocal. **Conclusión:** La ecografía transcutánea de laringe es un método no invasivo, sencillo de realizar, costo-efectivo y con resultados similares a la laringoscopía directa. Este procedimiento ecográfico no ha alcanzado aún una difusión masiva.

56593 THYROIDPRINT: A 10-GENE THYROID GENETIC CLASSIFIER (TGC) ACCURATELY PREDICTS BENIGN HISTOLOGY IN INDETERMINATE THYROID NODULES

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Introduction: In most of the world, diagnostic surgery remains as the most frequent approach for treatment of indeterminate thyroid nodules (ITN). Although, several molecular tests are available for central-lab testing in the US, there are no available diagnostic kits for local laboratory testing. To address this issue, we have developed and performed a clinical validity study of a 10-gene thyroid genetic classifier *in vitro* Diagnostic test (TGC-IVD) for ITN with a level of complexity such that it may be used in reference laboratories. **Methods:** We performed a 21-month, prospective, double-blinded, multi-center clinical validation study including 9 institutions, 2648 patients, 2982 fine-needle aspirations of which 565 (18,9%) were indeterminate (Bethesda III & IV). At the time of this analysis, the corresponding surgical pathology and adequate RNA was obtained for 193 samples. The expression of 10 genes was analyzed using a multiplexed q-PCR TGC-IVD and its performance was evaluated. **Results:** Of the 193 ITNs, 51 were malignant (cancer prevalence of 25.4%). The TGC-IVD correctly identified 47 of 51 malignant nodules, with a sensitivity of 92.2% (CI of 80%-98%), and specificity of 90.8% (95% CI of 84%-94%). The negative predictive values for follicular lesion or atypia of undetermined significance (Bethesda III) and follicular neoplasm (Bethesda IV) were 97.6% and 96.7%, respectively, whereas the positive predictive values were 77.8% and 78.6%, respectively. The TGC-IVD correctly predicted a case of medullary thyroid cancer as malignant. **Conclusions:** We report the clinical validation of a new TGC-IVD that accurately predicts the nature of indeterminate thyroid nodules and could be a future solution suitable for local reference laboratory testing, providing an accessible solution for clinicians to identify patients that can avoid diagnostic surgery.

56704 ULTRASOUND RATING SYSTEMS TO ASSESS THE RISK OF MALIGNANCY OF THYROID NODULES: COMPARISONS BETWEEN ATA'S GUIDELINE, AACE'S GUIDELINES AND TI-RADS

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Introduction: A gap in the reported malignancy risk between categories from recent ATA's and AACE's guidelines is noticed. In clinical practice some nodules are not included in both systems. **Objectives:** To compare different classification assessing malignancy risk of thyroid nodules. **Methods:** Thyroid nodules (n = 1554) were underwent fine needle aspiration and classified regarding ultrasound patterns in following classification systems: ATA's guideline, AACE's guidelines and TI-RADS. The major outcome was the frequency of malignancy, which was confirmed by histopathology for all Bethesda III, IV, V and VI nodules. A subgroup of nodules classified as Bethesda II also had histopathology or a second FNAB, confirming benign nature. Benign nature of Bethesda III and IV nodules was defined by histopathology, hyper function pattern on nuclear exams or confirmed reduction of > 50% on volume during follow-up. **Results:** Malignant outcome was confirmed in 292 nodules. The frequencies of nodules classified as probably benign, low risk, indeterminate risk and high risk according to ATA's guideline were: 0.1%, 53.5%, 31.4% and 15% respectively. The malignancy rates were respectively 3%, 14%, 40% and 100% for each ATA's category. Concerning AACE's classification 0.2% was Class 1 (malignancy rate: 0%), 76.1% Class 2 (malignancy rate: 6.9%) and 23.6% Class 3 (malignancy rate: 54.2%). The distribution of frequencies of nodules into TI-RADS categories was: 42.9% (TI-RADS 3 – probably benign), 32.2% (TI-RADS 4a – ow suspicion for malignancy), 17.5% (TI-RADS 4b – moderate risk for malignancy) and 7.4% (TI-RADS 5 – highly suggestive of malignancy). The frequency of malignancy increased according to TI-RADS classifications: 2.5%, 9.7%, 43.6% and 92%. Some nodules (10.7%) could not be categorized according to ATA's classification (e.g.: an isoechogenic nodule with microcalcification) and 9.7% did not match criteria for any category of AACE's classification, mainly those hypoechogenic nodules that were less echogenic than thyroid parenchyma but not hypoechogenic in comparison to pre-thyroid muscles. TI-RADS system comprises the malignancy risk of those nodules not included in ATA's classification (3%, 14%, 40% and 100%) and AACE's classification (2.5%, 10%, 43.6% and 92%). **Conclusion:** TI-RADS system assessed appropriately the malignancy risk in thyroid nodules, and about 10% non-contemplated nodules by ATA's or AACE's guidelines were involved as well.

55827 UTILITY OF CYTOLOGY NEEDLE WASHING THYROGLOBULIN FOR THE ETIOLOGICAL DIAGNOSIS OF THE THYROID NODULE

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The determination of thyroglobulin in samples obtained from the needle wash of cytology with fine needle has been incorporated as a new tool in the differential diagnosis of metastatic cervical lymphadenopathy, but its use in the diagnosis of the thyroid nodule has not been sufficiently investigated. **Objective:** To evaluate the utility of thyroglobulin obtained from needle washing, used in cytology for the etiological diagnosis of the thyroid nodule. **Method:** Tg was determined on 90 samples obtained from the cytology needle wash of patients with a single palpable thyroid nodule who attended the CAF consultation. The Mann-Whitney test or the Student's t test were used to compare the quantitative variables. Sensitivity and specificity were assessed with the ROC curve for the entire range of thyroglobulin values. **Results:** There were statistically significant differences ($p < 0.001$) in the Tg concentration between benign lesions (502.6 ng/mL) and malignant lesions (11.95 ng/mL). The area under the curve shows a high accuracy of the Tg determination for the differential diagnosis of the thyroid nodule. A cutoff value of 144.1 ng/mL was obtained with a sensitivity of 100%, specificity 98%, positive predictive value of 98% and negative of 100%. **Conclusion:** Determination of thyroglobulin in the cytology needle wash is useful in the differential diagnosis between a benign and malignant lesion, particularly if a value of 144.1 ng/ml is used.