IN WELL DIFFERENTIATED THYROID CANCER ANTITHYROGLOBULIN ANTIBODIES ARE ASSOCIATED WITH A MORE AGGRESSIVE DISEASE THAT MAY BE MASKED BY HASHIMOTOS THYROIDITIS

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Background: Thyroid cancer is the most common endocrine tumor. It appears to have a higher prevalance in Hahimoto's thyroiditis (HT), with more patients having positive antithyroid antibodies than the general population. There is a strong body of data supporting a protective role of HT, but a few trials have failed to show a similar corelation for antithyroid antibodies. Following excision of thyroid and tumoral tissue, antibodies levels decrease and disappear in most patients .

Objectives: Comparison between DTC patients with/without anti-thyroglobulin Ab (TgAb) and/or HT regarding the severity of disease and clinical outcome. In addition we aimed to examine the natural course of TgAb levels overtime.

Methods: This is a retrospective study using the Rabin Medical Center Thyroid Cancer Registry. Data was collected retroactively before 2005 and prospectively thereafter. The 753 patients compatible for the study's criteria were divided into four sub-groups, those with/without TgAb and/or HT at diagnosis. Data for comparison between the groups was gathered from patients computerized and hand written files.

Results: TgAbs were present in 12.4% (n=93; 62.4% of them with HT) and HT was present in 14.2% (n=107; 54% of them TgAb positive). TgAb positive patients have more lymph nodes involvement (OR 2.45, 95% CI 1.36-4.40) and persistent disease (OR 1.80, 95% CI 0.99-3.27) compared to TgAb negative; while HT patients have less lymph node involvement (OR 0.34, 95% CI 0.17-0.66) and less persistent disease (OR 0.48, 95% 0.24-0.93) compared to non-HT patients. The differences were more significant comparing TgAb positive/HT negative (n=35) to HT positive/TgAb negative (n-49) patients. During follow-up 42/50 patients (84%) who did not require additional therapies became free of positive Ab at a median time of 15 ± 3.5 months.

Conclusion: Our study suggests that TgAbs are associated with a more aggressive disease when HT patients are excluded.

NEONATAL HYPERTHYROTROPINEMIA IS ASSOCIATED WITH LOW BIRTH WEIGHT: A TWIN STUDY

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Context: Contradictory reports ascribe neonatal hyperhyrotropinemia to prematurity or small weight for gestational age. Objective: We aimed to evaluate the association between neonatal hyperthyrotropinemia and birth-weight, the recovery rate of the disorder and its possible association with perinatal stress. Design and Setting: Based on neonatal screening database, a retrospective twin-study was designed where within-pair differences in thyroid function were evaluated while controlling for differences in gestational age and thyroid affecting environmental confounders. Participants: 2609 twin pairs that were screened both for TSH and T4 over three years were included.

Major Outcome Measures: We evaluated TSH and T4 levels along with birth-weight, birth order, gender and 17-hydroxyprogesterone that was considered as a surrogate marker for stress.

Results: 156 twin pairs (7.2%) had neonatal hyperthyrotropinemia. Among these pairs, hyperthyrotropinemia was more prevalent in the smaller twins (64%; $p<0.001$), especially in the discordant pairs (76%; $p=0.001$). Most twins demonstrated a recovery within the first few weeks of life. 17-hydroxyprogetreone levels were similarly distributed between twins with and without hyperthyrotropinemia. In a cohort of 1534 twin pairs with normal thyroid function, mean TSH levels were significantly higher in the smaller- than in the larger-twin in the whole group (4.1±3.2 *vs.* 3.8±2.9 mIU/L; $p<0.001$) and especially among discordant twins (4.7±3.4 *vs.* 3.8±3.0 mIU/L; $p<0.001$).

Conclusions: Elevated TSH levels are associated with low birth-weight, both in infants with hyperthyrotropinemia and in neonates with normal thyroid function. A rapid recovery rate is expected in most cases. Hyperthyrotropinemia is apparently not stress related.

ESTABLISH AND CONFIRM THE UPPER LIMIT OF TSH REFERENCE RANGE

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Introduction: The TSH upper reference limit (URL) and its association with age was widely discussed in the last decade. Most publications reported upper limits in the range 3.5-4.5 mIU/L. Defining reference intervals (RI's) for laboratory tests is a complicated process and almost impossible for the clinical laboratory. Recently, several publications presented the Hoffmann method(1) as an achievable technique in community laboratories.

Target: Establish and confirm the TSH URL for Maccabi Health Care Services patients using Hoffmann's technique.

Method: Hoffman method enables determination of RI without selection of "healthy" subjects. This method is appropriate for community laboratories whose patients are basically healthy and for analytes with a Gaussian distribution. In this approach, outliers and “sick” populations are removed statistically by plotting the analyte value vs. % cumulative frequency. A straight line drawn through the central 50th percentile excludes the “sick” population at both ends of the graph. Extrapolation of the straight line to the 2.5 and 97.5 percentiles allows computation of the lower and upper reference limits.

TSH results (Siemens ADVIA Centaur) were collected from Maccabi Laboratory database: 56000 adults and 30000 children results. Hoffmann approach was applied on the data grouped by age.

Results: The age specific URL's are detailed in the following table:

Age	TSH Upper Reference (Limit (mIU/L
months 1-12	5.5
years 1-18	4.5
years 19-59	4.2
years 60-69	4.8
years 70-79	5.5
years 80<	6.3

Discussion: Retrospective analysis using Hoffmann technique establishes the age specific upper reference limits of TSH for Maccabi patients, which match published values. The adult TSH upper limit increases with age, similar to the NHANES-III study(2). The pediatric values correlate with the Hübner study(3)

References:

1. Hoffmann, JAMA 1963; 185, p864.
2. Boucai et al, Thyroid 2011; 21, p 5.
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CONGENITAL HYPOTHYROIDISM SCREENING TO DETECT ALSO HYPOPITUITARY HYPOTHYROIDISM

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Background: The Israli National Newborn Screening Program for Congenital Hypothyroidism (CH) was initiated in May 1978. The filter paper screening algorithm starts with the measurement of total T4 (TT4) followed by TSH. This approach has been aimed to identify infants with primary CH. However, it also has the potential of detecting secondary Hypopituitary Hypothyroidism (HH), infants with persistently low T4 concentrations.

Objective: A two year pilot study intended to detect infants with HH without increasing the burden of high recall rate was carryout.

Methods: Most infants with low TT4 are either premature or infants from known populations with high incidence of TBG deficiency. In our study full term infants with the combination of TT4 below 2.5 ug/dl together with TSH below 5 mIU/L were selected.

Results: Between February 2009 and December 2010 we have identified 17 newborns (16 M and 1 F, 10 Jews and 7 non-Jews) suspected for HH. The TT4 levels were between 0.95-2.5 ug/dl and TSH 0.1-2.5 mIU/L. The follow-up venous blood Free T4 concentrations were between 13.9-24.2 (median 16.5) pmol/L, and TSH 1.5-3 mIU/L. From the 17 identified only 1 infant had TSH pituitary hormone deficiency, 3 of the families had previously born infants with TBG deficiency.

Conclusions: The current method has the potential to identify infants with HH. It is very likely that less tight cutoff will yield more detectable HH for selected group of infants. It remains to determine the appropriate cutoff which will justify this screening method in conjunction with follow-up venous blood Free T4 and TSH.

RINSE-PTH OBTAINED VIA FINE NEEDLE ASPIRATION IN THE EVALUATION OF PRIMARY HYPERPARATHYROIDISM WITH CONCOMITANT THYROID NODULES: EXPERIENCE OF ONE CENTER

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Background: Diagnosing parathyroid adenoma [PTA] in the context of multi-nodular goiter [MNG] or Hashimoto disease is a challenge. In the work-up of patients with discordant finding between MIBI-SPECT and ultrasound [US] we implemented rinse-PTH [r-PTH] obtained via fine needle aspiration [FNA]. The aim of this study is to present our experience.

Methods: All the relevant patients during 2010-2011 were included. FNA and r-PTH were done under US-guidance from all suspected thyroid or parathyroid lesions. In cases when r-PTH values were less than 5000 pg/ml rinse-thyroglobulin [r-Tg] was also measured.

Results: We had 5 females and 4 males, age 60±12. In 3 patients 2 different lesions were examined. Five patients had r-PTH above 5000pg/ml. Their post-surgery pathology was cystic-PTA, intra-thyroid PTA, post-previous surgery distorted PTA, and 2 "simple" PTA. In one of the cases with the "simple" PTA, the r-PTH result helped in narrowing the extent of the surgery. In 3 patients r-PTH was below 30pg/ml and r-Tg normal. These patients are under further evaluation. The last patient had 2 lesions: a suspected PTA [by MIBI and US] and another lesion which was aspirated. The result; r-PTH-718 and r-Tg - 10.3ng/ml is high but inconclusive. That patient underwent excision of the highly suspicious lesion- it was PTA. But, she is still hypercalcemic with elevated PTH. This raises the possibility that the sampled lesion was a double and dormant PTA

Conclusion: In our hand r-PTH is a valuable tool for preoperative localization of PTA.

VITAMIN D LESS-CALCEMIC ANALOGJK 1624 F2-2 MODULATES MRNA EXPRESSION OF ERS AND 1OHASE IN HUMAN THYROID CANCER CELLS: IMPLICATION FOR THYROID CARCINOMA CELL GROWTH.

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Estrogen receptors (ERs) are expressed in various "non-reproductive" cancer cell types. Some cancer types express1α- hydroxylase 25- hydroxyvitamin D(1OHase) whose product, 1,25$(OH)_2D_3$ can inhibit cancer cell proliferation. Thyroid carcinoma cell growth is apparently promoted by estrogens, but whether or not this interaction is modified by vitamin D metabolites/analogs is presently unknown. Here we assessed the effect of a less calcemic vitamin D analog [JK 1624 F_2-2 (JFK)] in three human thyroid cancer cell lines: ARO (anaplastic carcinoma), NPA (papillary carcinoma) and MRO (follicular carcinoma).

First, all three cell lines expressed both ERαand ERβmRNA and 1OHaseas quantified by Real Time PCR. There was a general abundance of ERβ(over ERα expression, such that the ratio of ERβto ERα mRNA was >1000:1, 228:1 and 7.7:1 in ARO, MRO and NPA cells, respectively. JKF up regulated ERβexpression in ARO (by 110+15%) and in MRO (by 280+10%) but down regulated it in NPA cells (by40+15%). Second, all three human thyroid cancer cell lines were found to express1OHase. Further, the expression of 1OHasewas up regulated by JKF in MRO (350+25%) and NPA (35+8%) but down regulated in ARO (20+5%).

This is the first report to identify1OHasein human thyroid cancer cells. A functional role for this enzyme is suggested by the finding that the vitamin D analog can affect ER expression, which is involved in estrogen-induced cell growth in the same human thyroid cancer cell lines (JSBMB126:95, 2011).

RIGHT HEMICOLECTOMY IN THE TREATMENT OF PATIENTS WITH APPENDICEAL NEUROENDOCRINE TUMORS: DOES SIZE MATTER?

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Background: A recent study of a small series of patients with appendiceal neuroendocrine tumors (ANETs) revealed that approximately 25% may harbor identifiable extra-appendiceal disease. The residual disease might not have been detected using the latest European Neuroendocrine Tumors Society (ENETs) revised pathological criteria.

Aims: To evaluate the latest pathological criteria for completion right hemicolectomy in an extended series of patients with ANETs.

Methods: The medical files of 27 consecutive patients who underwent RHC for ANETs in three tertiary hospital NETs clinics were retrospectively assessed. Demographic, clinical and laboratory data were collected, and surgical specimens reviewed to assess the indications for RHC, as follows: tumor diameter of ≥2cm, tumor location at the appendiceal base, extensive mesoappendiceal invasion (EMI) of >3mm, vascular invasion (VI) or a KI67 proliferation index of ≥2%.

Results: 5/27 patients were found to have residual disease. In 8/27 patients (30%) the tumor diameter was less than 1 cm (mean 0.7±0.2cm, range 0.3-0.9 cm); the indications for RHC included: tumor presence in surgical margins (3), EMI (5), VI (2), KI67 ≥2% (3); residual disease was present in one patient (13%). In 12/27 patients (44%) the tumor diameter was 1-2 cm (mean 1.30±0.2cm, range 1.0-1.5 cm); the indications for RHC were as follows: tumor presence in surgical margins (1), EMI (10), VI (2), KI67 ≥2% (2); residual disease was present in two patients (17%). In 7/27 patients (26%) tumor diameter was ≥2 cm (mean 2.5±0.7cm, range 2.0-4.0 cm). In this subgroup, RHC is accepted practice; the tumor was present in surgical margins (3), EMI(7), VI (5), and KI67 ≥2% 5 patients; residual disease was present in two patients (28%).

Conclusions: In patients with ANETs it is well established that tumor size and EMI are the most significant factors in taking the decision about the extension of the surgery. Our data suggests that in the subgroup of patients with a primary tumor size between 1-2cm (the *"gray zone"*) the risk of residual disease high. Using the latest criteria for RHC, residual disease may be missed in 7% of ANETs patients.