

Polish Thyroid Association PTT 2011 3rd Meeting

Lectures and oral presentations

MOLECULAR MECHANISMS OF THYROID GLAND DISEASES

M. Karbownik-Lewińska, J. Nauman, S. Sporny

W1:

Thyronamines — Past, Present, and Future

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Thyronamines (TAM) represent a new class of thyroid hormone derived endogenous signalling compounds with remarkable biological effects on body temperature, energy metabolism, cardiac function and neurotransmission. TAM may be formed from their precursor iodothyronines via a combination of deiodinase and decarboxylase reactions in target tissues. No evidence for their *de novo* biosynthesis from tyrosine or tyramine and iodination of the iodine-free thyronamine (T0AM) has been presented so far. The three deiodinase selenoenzymes Dio1, Dio2 and Dio3 show distinct structure-activity relationships in deiodination of T4AM and its derivatives with lower iodine content. The putative decarboxylase(s) proposed to generate TAM from their corresponding iodothyronines is (are) still elusive. Human aromatic amino acid decarboxylase apparently does not produce TAM from iodothyronines. 3-Iodothyronamine (3T1AM) is the major TAM found in human and rodent serum and to some extent T0AM has been detected too. In serum 3T1AM is avidly bound to apolipoprotein B100, which might explain reported differences in 3T1AM serum levels and its remarkably long serum half-life. A significant amount of 3T1AM is generated in peripheral tissues as demonstrated in T4 substituted thyroidectomised patients. TAM is metabolized by amine oxidases to generate thyroacetic acids (TAC). TAM interfere with cellular uptake and efflux of iodothyronines catalyzed by various plasma membrane transporters. Nevertheless, significant uptake and cellular accumulation of TAM has been demonstrated. Whether 3T1AM exerts its biological effects via G-protein coupled cell membrane receptors of the trace amine associated receptor (TAAR) family as well as by interaction with cellular organelles such as mitochondria remains to be studied. Currently, a variety of marked effects on glucose and lipid metabolism, neurotransmitter transport and uptake, cardiac and metabolic parameters have been reported both at pharmacological and physiological concentration levels after peripheral or central administration of 3T1AM or T0AM in various animal models. More research is needed to better understand the physiological and pathophysiological role of TAM formation and action.

W2:

Molecular genetics of thyroid and polyglandular autoimmunity

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Polyglandular autoimmunity or failure encompasses various endocrine disorders of autoimmune origin with an onset in chil-

hood (the rare juvenile APS type I) or in adulthood (the more frequent APS type II and III). Autoimmune thyroid diseases (AITD) and type 1 diabetes (T1D) are the most common autoimmune endocrine disorders within the complex APS. They occur frequently together in the same individual. The disease combination is denominated as autoimmune polyglandular failure syndrome type 3 variant (APS3v).

Family and population studies showed that the APS3v syndrome has a strong genetic background. Whole genome and candidate gene approaches identified several gene variations which are present in both AITD and T1D. Most important common disease susceptibility genes are *HLA* (chromosome 6), *CTLA-4* (chromosome 2), *PTPN22* (chromosome 1), *FOXP3* (X chromosome) and the *IL-2Ralpha/CD25* gene region (chromosome 10), all of them contributing to the susceptibility to APS3v. With respect to the underlying pathogenetic mechanisms, these genes are altogether involved in the immune regulation, in particular in the immunological synapse and T-cell activation. In addition to these common genes, there are further candidate genes with joint risk for AITD and T1D, in particular the *ERBB3* gene (chromosome 12) and *CLEC16A* gene (chromosome 16). The latter one might be involved in pathogen recognition. AITD and T1D share common susceptibility gene variants which possibly act pleiotropically as risk factors for the development of autoimmunity in APS3v. The functional consequences of the genetic variants as well as their interactions should be explored in greater detail. In particular, the functional consequences of the variants of *FOXP3* predisposing to APS3v need to be elucidated. Finally, further large-scale genomewide associations studies of SNP variations capturing many thousand individual genetic profiles are warranted in order to identify further genes which are linked to the etiology of APS3v.

W3:

Molecular mechanisms of thyroid hormone action in thyroid gland

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Thyroid hormones, thyroxine (T4) and triiodothyronine (T3) are synthesized in thyroid gland in a multistep process in which several key proteins are involved: sodium-iodide symporter (NIS), pendrin (PDS), thyroperoxidase (TPO), and thyroglobulin (Tg). Thyroid hormones are synthesized under strict control of thyrotropin-stimulating hormone (TSH) which initiates cAMP signaling cascade and regulates the expression of NIS, PDS, TPO and Tg. The main source of T3 in thyroid gland in euthyroidism is hydrolysis of thyroglobulin. In hyperthyroidism the activity of iodothyronine deiodinases significantly contributes to overall thyroidal T3 production, reaching up to 50% of T3 produced in thyroid gland in severe hyperthyroidism.

Thyroid hormones regulated the expression of multiple genes via two mechanisms: genomic and non-genomic one. In the genomic

Table I. Genetic abnormalities depending on dysgenesis type

	♀ A	♀ A	♂ A	♀ E	♀ E	♂ E
PAX8	+			+		
TSHR		+			+	
FOXE1			+			
TPO					+	+

(A – thyroid agenesis, E – sublingual ectopic thyroid gland) and gender (♀ female, ♂ male)

mechanism thyroid hormones bind specific thyroid hormone receptors (TRs) which act as a ligand-dependent transcription factors. TRs bind to specific TRE sequences in promoters of T3-regulated genes and modify their transcription. In the non-genomic mechanism, apart from TRs, other receptors localized in plasma membrane and cytoplasm are involved. They induce signaling cascades which result in broad cellular effects including changes in expression of target genes, the activity of membrane channels, and changes in elements of cytoskeleton.

Disturbances in TRs were discovered in pathologies of thyroid gland, including thyroid neoplasia. In the latter, TRs' mutations and disturbances of expression were identified. Mouse models of thyroid cancer suggest that thyroid hormone receptors may function as tumor suppressor factors and mutations in TRs may initiate mechanisms leading to proliferation activation, apoptosis inhibition, and increased cell motility resulting in metastasis. The identification of TRs-dependent disturbances of signaling cascades offers therapeutic opportunities for thyroid cancer patients.

W4:

Detection of genetic abnormalities in children with congenital hypothyroidism using MLPA analysis

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Introduction: Thyroid dysgenesis (TD), usually sporadic, is the most common cause of congenital hypothyroidism (CH). Among genetic factors that may contribute to TD etiopathogenesis, the highest importance is ascribed to mutations of transcription factors and TSH receptorencoding genes.

Objective: Assessment of incidence of changes involving genes encoding PAX8, FOXE1, NKX2-1, TSHR detected by multiplex ligation-dependent probe amplification (MLPA) in CH and TD children.

Material and methods: Investigations included 46 children selected in mass screening tests between 1995 and 2009, in whom CH resulted from: ectopy (n = 17), agenesis (n = 22), thyroid hypoplasia (n = 7).

DNA was isolated from peripheral blood samples using Master Pure DNA Purification Kit (Epicentre Biotechnologies). 50–100 ng of genomic DNA was employed in MPLA analysis using a SALSA MLPA kit P319-A1 THYROID (MRC-Holland). Genetic changes were analyzed within selected fragments of the PAX8, FOXE1, NKX2-1, TSHR and TPO genes. Testing followed a standardized procedure provided by the manufacturer. Stages of MLPA analysis

included: DNA denaturation, MLPA probe hybridization, ligation, PCR reaction, separation of reaction products by capillary electrophoresis and data analysis.

Results: Four types of heterozygous deletions in probe hybridization regions were identified for the following genes: PAX8 in exon 7, TSHR in exon 2, FOXE1 in exon 1 and TPO in exon 16. Genetic abnormalities of selected gene fragments were identified in 6/46 subjects (Table I).

Conclusions: MLPA screening showed genetic abnormalities in 13% of CH and TD children, manifested as deletion at probe hybridization site. Precise determination of the character of such abnormalities and genotype-phenotype correlation requires extending the study of selected regions to include other molecular methods (Sanger sequencing).

W5:

First Announcement of Glucagonlike Peptide-1 Receptor Imaging Positive Results in Patients with Medullary Thyroid Carcinoma (MTC)

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Introduction: MTC accounts for 5–10% of all thyroid cancers. In some MTC patients with postoperative calcitonin elevation, basal or in pentagastrin test, and negative imaging technique results it is necessary to search for new targets for radioisotope diagnostic. Overexpression of GLP-1 receptors have been shown on different types of neoplastic cells, among others on parafollicular thyroid C-cells. The aim of this study was to present the preliminary experiences with the use of ^{99m}Tc-labeled GLP-1 analogue in MTC imaging.

Material and method: ^{99m}Tc-GLP-1 receptor scintigraphy with [Lys40(Ahx-HYNIC-^{99m}Tc/EDDA)NH2]-exendin-4 was performed in 3 patients. The first case: 70yo man, with dissemination of MTC (2008), treated with PRRT, local recurrence of MTC (2011). The second case: 66yo man, metastatic lesions of MTC in liver and lymph nodes (2009), treated with PRRT, since then stabilisation of the disease. The third case: 22yo man, with genetically confirmed MEN2a syndrome, suspicion of local recurrence after abnormal pentagastrin test (2009), thyroid US revealed hypogenic lesion with subsequent negative biopsy result. The lyophilized kit prepared by IAE POLATOM was used for preparing the tracer. WB scans were performed at 6 time points and SPECT at 3 points. The hybrid device SPECT/CT was used to perform examinations.

Results: In the first patient, recurrence of the disease was assumed after GLP-1 scintigraphy. In the second patient, a pathological tracer accumulation in the liver was found. For both patients the similar images to GLP-1 scintigraphy were obtained in SRS scintigraphy. In the third patient, the GLP-1 scintigraphy showed the tracer uptake in the same place as 99mTc and 131I

scans. The patient was qualified to neck surgery. In all patients no side effects after the labeled GLP-1 analogue injection were observed.

Conclusion: [Lys40(Ahx-HYNIC-99mTc/EDDA)NH2]-exendin-4 seems to be a promising new tracer for clinical practice in MTC patients, especially when standard imaging techniques fail.

AUTOIMMUNE THYROID DISEASES

E. Bar-Andziak, R. Junik, W. Zgliczyński

W6:

Oxidative stress and the thyroid gland

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Key words: thyroid; thyroid hormone synthesis; free radicals; hydrogen peroxide; iron; oxidative damage; antioxidant; thyroid cancer. Reactive oxygen species (ROS) and free radicals are formed in living organisms — in certain amounts — under physiological conditions. An overproduction of ROS and free radicals results in enhanced oxidative stress and can lead to several diseases. The most basic reaction of oxidative stress is Fenton reaction: $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^-$. Hydroxyl radical ($\cdot\text{OH}$), produced in this reaction, is the most toxic free radical.

Whereas oxidative reactions occur in practically all tissues and organs, the thyroid gland constitutes such an organ, in which ROS (and iron as well) are indispensable for hormone synthesis. Mechanisms of ROS generation in the thyroid gland are extensively examined, with NADPH oxidases possessing the primary role in intracellular H_2O_2 formation. Hydrogen peroxide is indispensable for thyroid hormone synthesis, serving as a limiting co-factor for thyroid peroxidase (TPO) at all steps of this process. Although not measured up to now, iron and H_2O_2 must be at very high concentrations in the thyroid gland, potentially creating conditions for huge oxidative stress. It is assumed, therefore, that the increased iron supply or the increased H_2O_2 production in the thyroid, resulting from redox imbalance, may lead to enhanced oxidative damage and consequently to initiation of different disorders, cancer included. It is hypothesized that oxidative stress possesses the primary role in thyroid cancer initiation.

W7:

Autoimmune disorders during pregnancy

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During pregnancy plenty of metabolic, hormonal and immunologic changes take place, that have significant influence on occurrence and course of autoimmune thyroid dysfunctions and also of other autoimmune disorders, such as Addison's disease, type 1 diabetes mellitus, systemic lupus erythematosus or rheumatoid arthritis. During pregnancy the physiologic immunosuppression develops, that concerns either the cellular response with following decrease of helpers lymphocytes to suppressor lymphocytes ratio, or the humoral, that is associated with a decrease of most antibodies concentration, including antithyroid antibodies. Induction of tolerance in the placenta-decidua space allows the pregnancy to develop although the fetus contains the unfamiliar for maternal organism antigens, which derive from father.

Mechanisms of this phenomenon are complicated. Trophoblast syncytium cells that contain big quantities of indoleamine 2,3-dioxygenase enzyme that is responsible for tryptophan degeneration, which lack prevents T-lymphocyte proliferation seem to be most significant in immunologic tolerance induction. The syncytiotrophoblast cells demonstrate the unique model of tissue compatibility antigens presentation: lack of classical MHC- HLA-A, HLA-B, HLA-DP, HLA-DQ and HLA-DR and presence of classical HLA-C and non-classical HLA-E and HLA-G antigens expression, that prevents the NK (Natural Killers) cells activation and CD8 cytotoxicity. Moreover, the syncytiotrophoblast cells express the Fas ligand with the following Fas binding on activated lymphocytes, that leads to lymphocyte death and binding with Fas of the complement system, that leads to its activation inhibition. The decidua is also of great importance in placenta-decidua space tolerance. It's actually known, that decidua is infiltrated with uterine NK cells, that are less cytotoxic and produce big amounts of immunoregulatory cytokins. The decidua is also infiltrated by the T-regulatory cells, that are significant in the embryo implantation process. The T-regulatory cells have ability to inhibit the other T cells proliferation and activation as well by the direct contact as by immunosuppressive IL-10 and TGF cytokins secretion. Reassuring, during pregnancy a systemic immunosuppression does not develop, but the state of selective, transient tolerance is formed. In the postpartum period the phenomenon of increased immunologic tolerance disappears and even a so called "rebound phenomenon" can develop, that causes the present before diseases exacerbation or new autoimmune diseases manifestation. Out of autoimmune thyroid diseases during pregnancy Graves-Basedow's and Hashimoto's diseases should be remembered about. Hyperthyroidism caused by Graves-Basedow's disease in the first pregnancy trimester can temporarily exacerbate, then a disease remission begins and the symptoms of hyperthyroidism decrease, that is significant in therapeutic decisions taking. Hypothyroidism caused by Hashimoto's disease, despite that the amount of antithyroid antibodies during pregnancy decreases, demands usually about 50% increase of substitutive thyroxin dose, that is necessary for the proper foetoplacental unit functioning.

W8:

Interleukin 1 beta (IL-1beta) gene polymorphisms (SNP-511 and SNP+3953) in Hashimoto's thyroiditis among the Polish population

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Objective: The role of cytokines in the pathogenesis of Hashimoto's thyroiditis (HT) is well confirmed, but association of certain cytokine genes polymorphisms with susceptibility and/or course of this disease needs further investigations. IL-1 beta which is produced in the HT thyroid may induce FAS expression in normal thyrocytes resulting in massive thyrocyte apoptosis and destruction. Previous studies did not reveal any association between selected SNPs of IL-1beta gene and susceptibility to HT among the Chinese and UK Caucasian population.

Aim: This study presents the association between the interleukin 1 beta (IL-1 beta) gene polymorphisms at -511 in the promoter region (SNP-511) and +3953 in exon 5 (SNP+3953) and susceptibility to the development of Hashimoto's thyroiditis among Caucasian-Polish population.

Patients and methods: The studied group comprised of 115 unrelated patients with HT (112 women and 3 men with a mean age of 53 years). All patients were euthyroid on thyroid replacement therapy, and all patients had extremely high serum anti-TPO levels and in 53 patients anti-Tg levels were also increased. The control group consisted of 103 healthy blood donors without raised anti-TPO antibodies, in whom a personal and a family history of thyroid and autoimmune as well as inflammatory diseases was excluded. No goiter or thyroid dysfunction was found. Two polymorphisms of the IL-1 beta (C-511T and C+3953T) were studied by PCRFLP analysis. To confirm the accuracy of the method employed, randomly selected patients were analyzed by direct sequencing.

Results: Both control allele frequencies were in Hardy-Weinberg equilibrium. The significant statistical differences between the frequency of C allele and T allele for both SNPs in the studied group and in the controls were found ($p = 0.008$; using the chisquare test). The frequencies of the genotype of C-511C compared to C-511T and T-511T as well as C+3953C compared to C+3953T and T+3953T were statistically significant ($p = 0.0190$ and $p = 0.0129$; using Fisher's exact probability test).

Conclusions: An association between the SNP of the IL-1 beta and susceptibility to Hashimoto's thyroiditis among the studied group of Caucasian-Polish population was found.

W9:

The mechanism of cytotoxic reaction of lymphocytes and plasma cells against thyrocytes in Hashimoto's thyroiditis

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Background: The aim of the study was to analyze of the cytotoxic mechanism of action the cell T and B subsets in the thyroid tissue in patients with Hashimoto's thyroiditis.

Methods: We have studied paraffin thyroid specimens obtained from children with Hashimoto's thyroiditis, and children without an autoimmune thyroid disease. The mononuclear T-cells were detected by CD3+, CD4+, CD8+ antibodies, and the B-cells by CD79 alpha+ antibodies (plasma cells) (DakoCytomation Denmark), and they were counted with Sony Colour Camera Exwave HAD MultiScan5 system. The specimens from each patient were routinely estimated and investigated under the electron microscope.

Results: In Hashimoto's thyroiditis we observed a statistically significant increase in T suppressor/cytotoxic cells CD8+ ($20.54 \pm 0.68\%$) and plasmocytes ($31.65 \pm 9.11\%$) in the case of low number of T helper cells CD4+ (0.93 ± 9.90) in the thyroid gland in comparison with children without AITD. The ultrastructural investigations showed the connections of cytotoxic synapse character between T-cells, plasmocytes, and thyrocytes leading to apoptosis of thyrocytes. The thyrocytes were damaged in course of cytotoxic reactions. The second mechanism leading to the apoptosis — the production of collagen fibres by fibroblasts and considerable thickening of basal membranes of the thyroid follicles.

Conclusions: In Hashimoto's thyroiditis, autoantigen presentation in the case of low number of CD4+ T helper cells and increase in the number of CD8+ cells and plasmocytes, leads to cytotoxic reaction against thyrocytes. The direct contact of T-cells and plasma cells leads to apoptosis of the thyrocytes. The fibroblasts are involved in this process.

THYROID CANCER

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W10:

Identification and protection of important anatomical structures of the neck during thyroidectomy

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The superior and inferior parathyroid glands should be identified and preserved before resection of the thyroid gland. The superior parathyroid gland is normally present approximately 1 cm superior to the junction of the recurrent laryngeal nerve and the inferior thyroid artery. The inferior parathyroids are typically found within 1 cm of the lower pole. Over 80% of superior parathyroids supply and almost 90% of inferior parathyroid supply is coming from inferior thyroid arteries. Recurrent laryngeal nerve on both sides should be identified before dissection of the thyroid.

Intraoperative neural monitoring is very helpful especially in cases in which the visual information is problematic. Routine visual identification of the recurrent laryngeal nerve reduces the incidence

of injury. After identification and prevention of important anatomical structures of the neck total thyroidectomy is safety done by the surgeons.

W11:

Fine-needle aspiration biopsy (FNAB) of the thyroid gland — from pure morphology and morphometry to molecular diagnostics

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The main goal of diagnostics of thyroid lesions comprises the differentiation between benign and malignant ones, i.e., determination of nature of the punctured lesions, and — in consequence — selection of a group of patients in whom surgical treatment is necessary. During this diagnostic procedure, it becomes possible to aspirate fluid from cystic lesions in the gland. The ultrasonographic (US)-guidance of fine-needle aspiration biopsy (FNAB) is absolutely

required and the main goal of US is a selection of the optimal area for FNAB, by monitoring the location of the tip of biopsy needle. It should be emphasized that there is a new approach to the criteria of typing dominant nodules, selected for puncture during FNAB. Namely, the most important is the pattern of blood flow in the lesion and US features of nodule/focus (associated with malignancy or suggesting rather a benign lesion), and not the diameter of nodule or its consistency, evaluated during palpation.

The American and European Thyroid Associations (including the Polish Thyroid Association), as well as the Polish Group for Endocrine Tumors, recommend to perform FNAB of foci with a diameter of 10 mm and larger, and also with a diameter less than 10 mm in patients with significant clinical risk factors for the presence of thyroid cancer, including patients with a history of family incidence of the disease in question, also in patients who were previously exposed to irradiation, and — as already mentioned — in all the patients with suspicious features in US image. There is controversy regarding the usefulness of individual parameters of ultrasound image (shape, echogenicity, irregular margins, the presence of calcifications, or pattern of the blood flow) in selecting foci for diagnostic puncture. It should be noted that FNAB is also helpful in establishing the diagnosis in cases of thyroiditis.

In order to increase the diagnostic efficacy of the thyroid cytological examination, various methods improving the evaluation of the obtained material have been employed. Some of those methods, including computerized image analysis, add quantitative assessment to routine qualitative evaluation performed by cytopathologists. Some other methods employ additional immunocytological or other specific staining. These methods allow determination of detailed histogenesis of aspirated cells, and, in some cases, the distinguishing between malignant and benign lesions. Molecular biology techniques are also used for that purpose.

Nowadays, the development of novel techniques of RNA storing and isolation enables elimination of extra punctures and proves diagnostic utility of a small number of cells remaining in the biopsy needle after routine cytological smear. New methods of molecular biology are of such sensitivity that they allow obtaining an unambiguous diagnosis even when aspirates are assessed as inadequate or undetermined for cytological analysis.

W12: Polish guideline on treatment of thyroid cancer

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Thyroid carcinoma is rare among human malignancies (< 1%), but is the most frequent endocrine cancer, accounting for about 5% of thyroid nodules. More than 75% of malignant nodules are differentiated thyroid cancer of the follicular epithelium (papillary and follicular). Diagnosis and treatment of thyroid carcinoma requires a multidisciplinary approach. First Polish guidelines for diagnosis and treatment of thyroid cancer were developed in 1995 and later in 2000 and 2006 updated. Current strategies for the diagnosis and treatment of thyroid cancer in Poland were summarized during IV Thyroid Cancer Conference in Zakopane last year. Herein we discuss the guidelines with respect to Polish experiences in diagnosis and treatment of thyroid cancer.

Fine needle aspiration biopsy remains the main tool to assess risk of malignancy in thyroid nodules. The newest guidelines underline the role of neck ultrasound to assess the risk of malignancy and to select most suspicious nodules for cytological examination.

Six categories of diagnostic classification scheme, which apart from malignant lesion introduces category of “suspicious for malignancy” has been introduced in the newest guidelines. In therapy, complete thyroidectomy is recommended for all thyroid cancer except for papillary thyroid cancer with diameter not exceeding 1 cm. Later on those patients are candidates for adjuvant radioiodine treatment. Adjuvant radioiodine treatment is recommended not only in treatment of locally advanced cancer (lymph node metastases or primary tumor in stage pT3-4) but also in patients with early cancer (pT2N0).

This recommendation is based on good results of Polish clinical studies. Development of new positron emission tomography centers enabled to recommend PET/CT examination in follow-up of patients with suspicion for metastatic disease.

W13: Intraoperative neuromonitoring of the recurrent laryngeal nerves may improve outcomes of surgery for well-differentiated thyroid cancer

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Background: The recurrent laryngeal nerve (RLN) is particularly prone to injury during thyroidectomy in a case of extralaryngeal bifurcation being present in approximately one-third of patients near the inferior thyroid artery or ligament of Berry.

Aims: Meticulous surgical dissection in this area may be additionally facilitated by use of intraoperative neuromonitoring (IONM) to assure safe and complete operation. The present study was undertaken to test this hypothesis.

Material and methods: A retrospective cohort study. The outcomes of total thyroidectomy with level VI lymph node clearance for well-differentiated thyroid cancer (WDTC; pT1-3,N0-1,M0) were compared between 225 patients undergoing surgery with IONM (2005–2009) and 225 patients undergoing surgery without IONM (2003–2005). The anatomical course of the extralaryngeal part of the RLNs were analyzed in detail in each operation. Two to 4 months after surgery, 24-hour thyroid iodine-131 (I-131) uptake was measured.

Results: Among patients operated with vs. without IONM the early RLN injury rate was 3.1% vs. 6.7% ($p = 0.01$), including 1.8% vs. 4.9% ($p = 0.01$) of temporary nerve lesions, and 1.3% vs. 1.8% of permanent nerve events ($p = 0.70$), respectively. Extralaryngeal bifurcation of the RLN was identified in 65 (28.9%) vs. 39 (17.3%) of patients operated with vs. without IONM, respectively ($p = 0.001$). Mean I-131 uptake following total thyroidectomy with vs. without IONM was $0.61 \pm 0.38\%$ vs. $1.57 \pm 0.67\%$ ($p < 0.001$). I-131 uptake lower than 1% was found in 168 (74.7%) vs. 54 (24%) patients operated with vs. without IONM, respectively ($p < 0.001$).

Conclusions: Most patients with WDTC who undergo total thyroidectomy have a small amount of residual thyroid tissue. Use of IONM may improve outcomes of surgery among these patients by both increasing the completeness of total thyroidectomy and significant reduction in the prevalence of temporary RLN injury. The possible mechanism of this improvement is the aid in dissection at the level of Berry’s ligament offered by IONM which enhances the surgeon’s ability to identify a branched RLN, and allows for reduction of traction injury and neuropraxia of the anterior branch of bifid nerve.

PRESENT CHALLENGES IN THYROIDOLOGY

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W14:

Treatment of metastatic thyroid cancer

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The large majority (> 85%) of patients with differentiated thyroid carcinoma (DTC) and many (40%) patients with medullary thyroid carcinoma (MTC) can be cured, others may survive for decades despite persistent disease, and few patients with advanced disease may require novel therapeutic modalities. Very few patients with anaplastic carcinoma survive over one year.

Distant metastases occur in 5–10% of DTC patients and one third of such patients can be cured with a combination of levothyroxine treatment at doses that suppress TSH secretion, radioiodine treatment and local therapeutic interventions. Prognostic indicators for response are younger age, well differentiated thyroid tumor, small size of metastases, high uptake of radioiodine and low uptake of FDG on PET scan. Refractory thyroid cancer patients are rare, with an estimated annual incidence in France of 350 cases that is stable with time, including 200 patients with DTC, 50 with MTC and 100 patients with anaplastic thyroid carcinoma. In most patients, an initiating carcinogenic event can be found and molecular targeted therapy can be given with a scientific rationale. Patients with progressive thyroid cancer should preferably be included in prospective trials, and even phase I trials that are testing the newest therapies should be considered for these patients, as these protocols may allow early identification of possibly effective drugs. Progression should be defined according to RECIST, and trends in serum tumor marker levels are not sufficient to define progression or to assess tumor response during treatment.

Although response criteria in these contemporary trials differ markedly from those evaluating cytotoxic chemotherapy, anti-tumour efficacy of these agents in MTC patients is likely to be much greater than that of earlier chemotherapies (ORR < 20% with chemotherapy using 5FU-DTIC). Tumour response rates are similar in lymph nodes, and lung, liver and bone metastases, and were similar in patients with smaller or larger tumour masses. Serum calcitonin and CEA levels decreased during treatment in most patients, and this indicates an inhibition of the RET kinase, but it may be not paralleled by a decrease in tumour volume. Comparison of the outcome among these compounds is at the present time not possible. Toxicity was significant and led to dose reduction in 11–73% of patients and to drug withdrawal in 7–25%. There were no unexpected toxicities with long-term treatment. However, there was no significant unexpected toxicity, and the dose of l-thyroxine treatment had to be increased in the majority of patients. Benefits demonstrated with vandetanib in a randomised phase III trial on both ORR (44% with long lasting responses) and PFS (> 30.5 months in the treatment arm (median not reached) versus 19.3 months in the placebo arm) counterbalance toxic effects and justify its use in MTC patients with progressive or symptomatic disease and those with large tumour burden. Vandetanib is available in France within the framework of an Autorisation Temporaire d'Utilisation (ATU) and has been labelled in the USA by the FDA. Results of the ongoing phase III trial with XL-184 are expected to confirm promising results obtained in the phase I trial in which 29% of 35 patients had a confirmed partial tumour response. There is apparently no cross resistance

between drugs. Drugs used up to now have similar mechanisms of action, all being anti-angiogenic and some (including vandetanib and XL-184) targeting the RET tyrosine kinase. The relative role of the inhibition of each target or of their combined inhibition is currently unknown, but because axitinib and pazopanib are thought to be only anti-angiogenic drugs, responses suggest that the anti-angiogenic effects of these compounds might play an important role. Also, responses to vandetanib or XL-184 have been observed in patients without RET mutation. Even among patients with an RET mutation, tumour responses were partial and were observed in only a fraction of patients. This may indicate that targeting RET may not be sufficient in all MTC patients. Future studies should explore the interest in effective inhibition of the MAPkinase pathway downstream of the RET kinase, and of other pathways such as the PI3K-AKT-mTOR pathway, and search for other relevant targets that may indicate the use of other drugs. In DTC patients, refractory disease is defined by the presence of at least one tumour focus without any uptake of radioiodine, or by progressive disease following radioiodine treatment or by persistent disease after six treatments with radioiodine. Among these cancers, histology (papillary and variants, follicular and poorly differentiated) and genetic defects may differ. Anti-tumour efficacy of these agents is likely to be greater than that of earlier chemotherapies (using doxorubicin or taxanes), with partial responses observed in 8–32% of patients and long-term stable disease in at least another half. Comparison of the outcome among these compounds is at the present time not possible, but the response rates recently reported with pazopanib and lenvatinib (E7080) (around 50%) seem higher than in previous reports. It also appears that efficacy may differ among histological subtypes, but further studies are needed to correlate drug efficacy with the genetic defect present in the tumour. Only results of phase II trials have been reported; a phase III trial (sorafenib vs. placebo) is ongoing and a phase III trial (lenvatinib vs. placebo) will be activated in 2011, as well as several phase II trials. Also, the stability of response and patterns of relapse have not been well characterised. Drugs used up to now have similar mechanisms of action, all being anti-angiogenic and some targeting the kinases in the MAPkinase pathway. Tumour responses were partial and transient and were observed in only a fraction of patients. This may indicate that future studies should use drugs targeted to already known abnormalities (such as an inhibitor of the BRAF kinase in patients with a papillary thyroid carcinoma harbouring the mutated BRAF), and search for other relevant targets. Given the commercial availability of sorafenib and sunitinib, these agents have entered into clinical use for those patients with progressive, refractory disease who are not suitable candidates for clinical trials. Finally, trials should be performed in patients with anaplastic thyroid carcinoma, using drugs directed against angiogenesis or other targets. Further trials should also search in MTC and DTC patients for other treatment modalities, including combination or sequential treatment. Recent trials have shown that inclusion of the expected number of thyroid cancer patients to reach statistically significant conclusions is possible in a limited period of time, and this may be further improved by networks such as the French TUTHYREF network and organisations such as the Endocrine taskforce of the EORTC.

Conflicts of Interest

Author has received grants and research funding from Amgen, Astra-Zeneca, Bayer, Esai, Exelixis and Genzyme.

W15: Selenium and the Thyroid

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The trace element selenium (Se), which is in the form of selenocysteine (Seys) inserted in selenoproteins, such as deiodinases, thioredoxins reductase and glutathione peroxidase, regulates synthesis and intra-conversion of T4 to T3 as well as redox control. Its deficiency has been associated with thyroid autoimmune disease and goiter. Se is abundantly present in the thyroid, made available via the main transporter of the mineral, Selenoprotein P (SeP), deficiency of the latter leading to disease. In addition, recently a report emerged concerning an inherited Secys defect, through a mutation of Secys Binding Protein, which disrupts thyroid metabolism. Se compounds in the form of selenomethionine or selenite have been therapeutically applied in patients with autoimmune thyroiditis exhibiting variable results as regards anti-TPO response and its anti-inflammatory effect, the discrepancy of the results possibly being dependent on the basal Se levels, the severity of disease and the duration of treatment. Studies have also reported a positive effect in patients with thyroid associated ophthalmopathy (TAO), containment of an exacerbation of TAO and prolongation of the remission phase in Graves' disease following withdrawal of anti-thyroid treatment. In pregnant women with autoimmune thyroiditis selenium administration is promising in reducing the incidence of miscarriage and the incidence of post-partum thyroiditis. As a micromineral in our daily diet, Se is of considerable importance for the prevention of oxidative stress and chemoprevention, while the maintenance of "selenostasis" is essential for preservation of human health.

W16: New aspects of autoimmune thyroid diseases including Hashimoto's and Graves' disease

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Thyroid autoimmune diseases include chronic lymphocytic thyroiditis with and without goiter, immunogenic thyrotoxicosis with or without thyroid associated ophthalmopathy (Graves' disease), post-partum thyroiditis and the very rare fibrosclerosing thyroiditis (Riedel's thyroiditis). Thyroid specific auto antibodies are frequently detected in otherwise healthy subjects (AIT) and affect around 16–20% of all females and up to 10% of males, increasing with age. However not all of these subjects develop an autoimmune thyroid disease (AITD), sometimes only after decades or never. In epidemiological studies it has been shown that 80/100,000 males and 350/100,000 females per year are developing hypothyroidism and 8/100,000 males and 80/100,000 females hyperthyroidism. The main cause of subclinical or overt hypothyroidism worldwide is Hashimoto's thyroiditis and no longer iodine deficiency.

The thyroid obviously is the organ which is highly vulnerable to autoimmune diseases (AITD). They develop due to the complex interplay of genetic, environmental, and endogenous factors, and a specific combination is required to initiate and promote autoimmunity. Seven genes had been identified that contribute to the etiology of AITD. HLA-DR3 is associated with Graves' disease and Hashimoto's disease. Non-MHC genes that confer susceptibility can be classified into two groups: immune-regulatory genes like CD40, CTLA-4, FCRL3, IL-2-R and PTPN22 and thyroid specific genes, the thyroglobuline and TSH-receptor genes.

Environmental factors that trigger the AIT are stress, unopposed high estrogens by progesterone, high iodine intake, selenium deficiency, pollutants, infectious diseases, and certain drugs like amiodarone or interferon-alpha. When the thyroid cell becomes the target of autoimmunity it interacts with the immune system, releases cytokines, growth factors, adhesion molecules which might promote the progression of the disease. A cooccurrence of AIT with differentiated thyroid carcinoma, especially papillary thyroid cancer (PTC) has repeatedly reported. It is still a matter of debate whether the chronic lymphocytic reaction is triggered by the malignant cells or vice versa. A higher frequency of malignancy of neoplastic thyroid nodules has been shown in several studies but not confirmed by others. The thyroglobuline antibodies seem to be unspecific, however TPO-antibodies are specific, their activity is associated with the activity of the disease, are complement activating, induce the antigen-presentation to autoaggressive T-cells, activate NK-cells but do not inhibit the enzyme activity. TSH-receptor antibodies (TRAb) either stimulate the thyroid function or only bind or inhibit the receptor.

Although the thyroid is the most common target of autoimmunity, other organs like islet cells, adrenal, gastric parietal cells, melanocytes of the skin, pituitary cells, or gonadal cells also might be affected although to less degree. This however has to be kept in mind for patients care. It also is important to consider family screening for thyroid diseases if one member has been identified to suffer from AITD as it has been shown that 7.5% of children within every 5 years from mothers with AITD develop thyroid specific antibodies. Females in child bearing age with positive thyroid specific antibodies but normal thyroid function (AIT) exhibit a 2–3 fold higher incidence of early abortion and premature delivery. These females have to be treated early with L-Thyroxine to keep TSH within the low normal range and a selenium supplementation might reduce the exacerbation of AITD after delivery. In contrast it is not justified to supplement L-Thyroxine in subjects with AIT but normal thyroid function as it has not been shown by controlled trials to influence of the course of the disease. These subjects might benefit from a selenium supplementation and avoidance of other environmental factors known to trigger or promote the disease. In Graves' disease, methimazole is the treatment of choice for about one year and the decrease of TRAb predict, whether thereafter the disease will relapse or not. If TRAb is above 10 U/L the probability of a relapse is more than 50% and thyroidectomy either by surgery or radioiodine treatment is recommended.

W17: Thyroid dysfunction associated with the administration of medications, including amiodarone and tyrosine kinase inhibitors

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For the last several decades some drugs have been used in the nonthyroidal disease treatment which present clinically relevant side effects on thyroid function. Some of them influence thyroid hormone metabolism changing the required supplementation dose of l-thyroxin in patients on the replacement therapy. Others affect hormone synthesis leading to the development of primary hypothyroidism. The immunomodulation medications and these used in anti-cancer therapy can also cause hypo- and hyperthyroidism with not fully known immunological and non-immunological mechanisms.

The best known are side effects associated with administration of amiodarone affecting approximately 15 to 20% of treated patients. Although, in spite of many studies, its influence on thyroid function remains unclear because of the process complexity. The least controversial is treatment of hypothyroidism caused by amiodarone, but some doubts may arise concerning the selection of the optimal l-thyroxine dose in case of sustained high values of both TSH and FT4. Amiodarone-induced thyrotoxicosis (AIT), more often observed in iodine-deficient areas, may occur at any time from the drug implementation, and, what is most important causes deterioration of the patient's cardiac condition. There are 3 types of AIT: type I is a consequence of a large amount of iodine load in patients with thyroid pathology, type II is a result of direct toxic effect of iodine/amiodarone on the thyroid cells causing destructive thyrotoxicosis, and type

III is a mixed/indefinite form which may have features of both AIT subtypes. Whereas some AIT cases are mild, others can be severe with a fatal outcome. The most controversial is recognition of AIT subtype and to find the best treatment method with the assessment of indications and an optimal time for surgery. Tyrosine kinase inhibitors (TKI) are increasingly being introduced for the treatment of cancer, and a lot of clinical trials have been conducted to assess their effectiveness in many different tumour types. According to the literature hypothyroidism may occur in up to 68% of TKI treated patients and thyrotoxicosis is observed in more than 20% of cases. During the course of TKI treatment hypothyroidism requires supplementation therapy with individually matched dose of l-thyroxine, and the open question remains whether hyperthyroidism is an indication for TKI therapy interruption, temporary discontinuation or lowering the dose of the drug.

Poster session

P1:

Medullary thyroid carcinoma — future possibilities of diagnosis and therapy

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Medullary thyroid cancer (MTC) is an uncommon malignancy arising from the parafollicular C cells. Its low incidence has limited both widespread clinical expertise and definitive large randomized clinical trials. Epidemiological studies have shown that during the past 30 years neither a change in stage at diagnosis nor improvement in survival has occurred for MTC patients. Current therapy of metastatic patients is not fully successful and searching for new therapies is necessary based on tumor biology (targeted therapy), and based on the interactions between thyroid cancer cells and their microenvironment (inhibitors of tumour angiogenesis). In recent years, the clinical validation of molecular targeted therapies has been one of the most exciting developments in cancer research and MTC represents a promising model. It is well known that in MTC, the tyrosine kinase RET (RET-TK) receptor and its signal transduction pathways, lead to subsequent neoplastic transformation. Several strategies aimed at blocking the activation and signaling of RET have been preclinically tested. The most advanced results have been obtained by competitive inhibition of RET-TK activity by tyrosine kinases inhibitors (TKI). However, although the inhibition of the RET pathway is actually one of the most studied for therapeutic purposes, other signal transduction pathways have been recognized to contribute to the growth and functional activity of MTC and are considered attractive therapeutic targets (mTOR inhibitors). To date, surgery represents the only curative treatment of MTC. Despite promising initial results, studies on targeted agents are in early stages and several issues regarding preclinical evaluations and clinical trials of new targeted agents in MTC are still unresolved. New hopes are concerned with radionuclide targeted therapy, especially with radiolabelled gastrin/CCK peptides.

A major effort needs to be made by endocrinologists, oncologists and nuclear medicine doctors to refer their patients for multi-institutional trials in order to optimize them, perform translational studies and expedite the availability of novel beneficial selective therapies.

P2:

The co-existence of papillary thyroid carcinoma and primary hyperparathyroidism in a female patient with toxic nodular goitre

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Introduction: The reason why differentiated thyroid cancer and primary hyperparathyroidism co-occur remains controversial. According to some authors, their coexistence is accidental, while others claim that it is caused by a high concentration of endogenous calcium and calcitonin. Nodular goitre is found in 22% to 70% patients with primary hyperparathyroidism. The incidence of carcinoma from thyroid follicular cells in patients with primary hyperparathyroidism is estimated at 3.1 to 15%.

Aim: To present a rare case of co-existence of papillary thyroid carcinoma and primary hyperparathyroidism in a female patient with toxic nodular goitre.

Case report: The patient, aged 75, has been treated for osteoporosis for several years. A thyroid ultrasound showed a toxic nodular goitre. A thyroid hormone test confirmed hyperthyroidism. An FNAB of one of the focal thyroid lesions showed tumour tissue composed of oxyphil cells. Hypercalcemia was revealed in a screening blood test. A clinical examination confirmed the diagnosis of primary hyperparathyroidism (hypercalcemia, hypophosphatemia, hypercalciuria and an elevated PTH level). An adenoma was found in the upper right parathyroid in MIBI scintigraphy. The patient underwent a thyroidectomy and a parathyroidectomy simultaneously. A post-operative histopathological test showed the following: a papillary thyroid carcinoma, invasion of the cancer into the thyroid capsule and local adipose tissue, lymphangiosis carcinomatosa and a parathyroid adenoma. There were complications in the post-operative period in the form of hypoparathyroidism with tetany, hypothyroidism and paresis of the left part of the larynx.

Conclusion: The co-existence of follicular thyroid carcinoma with parathyroid carcinoma is rare, but it needs to be taken into consideration in diagnosing thyroid diseases which often accompany primary hyperparathyroidism.

P3:**Thyroid metastases from a breast cancer diagnosed by fine-needle aspiration biopsy. Case report and overview of the literature***K. Łączka¹, D. Breborowicz², A. Uliasz³, M. Teresiak⁴*¹Department of Endocrinology, Metabolism and Internal Medicine, University of Medical Sciences, Poznan, Poland²Department of Tumor Pathology, Oncology Center, Poznan, Poland³Student's Scientific Society, University of Medical Sciences, Poznan, Poland⁴Department of Oncology Surgery, Oncology Center, Poznan, Poland**Key words:** thyroid metastasis, breast cancer, markers, fine-needle aspiration.**Objective:** Intrathyroid metastases are uncommon in cytology practice. We report a case of metastatic lesion in the thyroid from breast carcinoma which was recognized in fine needle aspiration biopsy (FNA) and confirmed by immunohistopathology. In addition, we provide an overview of literature describing similar cases.**Study design:** The patient was a 54-year old woman with a large, multinodular goiter and bilaterally enlarged lymph nodes in supraclavicular areas. Fourteen years earlier she had undergone radical mastectomy followed by chemo- and radiotherapy due to breast carcinoma.**Results:** FNA of thyroid nodules showed metastatic breast carcinoma and was followed by total strumectomy and lymphadenectomy. Histological reassessment of the surgical specimens of the thyroid gland as well as neck lymph nodes revealed multiple breast metastases. This was strongly confirmed by immunochemistry, which revealed the positive staining for: ER, PgR and HER2 as well as for CKMN16, CK7, and CEA, and negative staining for: thyroglobulin, TTF1, calcitonin, chromogranin and CK20.**Conclusion:** In view of the above, we deduce that every new aggregate in the thyroid in patient with even distant history of cancer should be considered as potentially metastatic until proved otherwise. FNA could be helpful in the diagnosis of the thyroid metastatic lesion.**P4: Hormonal activity of the thyroid gland in women after mastectomy treated with radiotherapy — personal research***A. Majkowska-Młynarczyk¹, M. Kinalski²*¹Faculty of Health — Higher School of Economy and Law Kielce, Provincial Specialist Hospital, Kielce²Provincial Specialist Hospital—Gynecological Department, Białystok

There is ongoing debate about the link between breast diseases and hormonal function of thyroid gland. Less information is present about influence of breast cancer treatment: mastectomy, radiotherapy, hormonal therapy or combined therapy on thyroid dysfunction. This work presents influence of aggressive form breast cancer treatment such as mastectomy and radiotherapy combined with chemotherapy on change in thyroid function just after finishing therapy and after five and 10 years from this moment. 173 women (mean age 56) were examined divided into breast cancer group — 97 women and control group — 76 healthy women. 27% women with breast cancer were treated with mixed beam photon-electron radiotherapy fractionated in 2.25 Gy doses to cumulative dose 45 Gy.

Thyroid function and morphology were diagnosed with:

1. Fine needle aspiration biopsy and USG with dynamic color-doppler mode

2. Measurement of hormone concentrations: TSH, FT3, FT4

3. Levels of antibodies: against thyroperoxidase and antithyroglobulin

Results show that in the group after radiotherapy levels (arithmetic mean) of anti-TPO are two times higher in the group after radiotherapy. In 46% of patients levels of anti-TPO were higher but median levels don't show statistical difference. Antithyroglobulin antibodies were higher in 20% of women treated with radiotherapy. There was no influence of radiotherapy on thyroid hormone concentrations. Papillary carcinoma of thyroid gland was found in two patients, which is 7% of patients treated with radiotherapy.**Conclusions:** 1. Previous breast cancer treatment (chemotherapy, radiotherapy) results in increased levels antithyropoxidase antibodies. 2. Radiotherapy of breast cancer can increase prevalence of thyroid cancer. 3. Women after successful breast cancer treatment have high levels of thyroid antibodies. It can suggest that after years it could manifest with laboratory and clinical signs of thyroid insufficiency.**P5: Thyroid lymphoma — diagnostic struggle***A. Łuczycycki¹, E. Koperski³, M. Januszewicz³, J. Pachucki¹*¹Department of Internal Medicine and Endocrinology, Medical University, Warsaw²Department of Pathological Anatomy, Center for Biostructure Research, Medical University of Warsaw³II Department of Clinical Radiology, Medical University, Warsaw

We present a case report to dispute diagnostic difficulties in patients suspected for thyroid lymphoma.

This 68-yo man was sent to ER from endocrinology clinic due to symptoms of upper airway obstruction and asymmetrical rapid (few weeks) increase in goiter size. Patient's symptoms were obscured by severe COPD which required several admissions over last few years. He was previously followed for years due to non-toxic MNG but FNAB was probably never done before. Three months earlier when large B-cell lymphoma was diagnosed after removal left testicular tumor (about 8 cm) and endocrine consultation recommended methimazole for thyrotoxicosis although no clinical suspicion of thyroid malignancy was appreciated. At admission the thyroid was hard and tender but without redness, surrounding soft tissue edema or pathological lymphatic nodes on palpation. Thyroid ultrasound suggested multinodular goiter with nodule conglomerates up to 4.5 cm. The FNAB of dominant nodule suggested thyroiditis. Patient was sent home on low dose steroids. Due to diagnostic bias three consecutive FNAB were performed by three pathologists and two of them described inflammation and one atypical cells probably lymphoid in origin (flow cytometry was non diagnostic due to low leukocyte count).

Symptoms did not improve and total body CT showed oval areas of infiltration in liver and lung very suggestive for malignancy. Moreover tracheo-nodal or tracheo-thyroid fistula was suspected based on CT and bronchoscopy (biopsy of tracheal exophytic mass was non-diagnostic). FNAB of liver lesion was highly suggestive for lymphoma and patient received Dexamethasone and one course of COP chemotherapy. Follow up bronchoscopy showed increase in size of exophytic mass but biopsy was again non-diagnostic. Patient was sent home and further chemotherapy was withheld awaiting clarification of single positive sputum smear for AFB (MTb-PCR negative). Four months from stepping into ER, shortly after following admission patient died probably as a result of pneumothorax and worsened respiratory failure. Thyroid FNAB has limited value in diagnosing of thyroid lymphoma.

P6: Cigarette smoking as a risk factor for differentiated thyroid cancer

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The aim of the study was to assess the association of tobacco smoking with differentiated thyroid cancer (DTC).

Material and methods: The “case-control” study was performed in 232 patients with DTC: in 31 men (mean age 60.2 ± 12 years) and 201 women (mean age 50.7 ± 13.1 years) and in 342 healthy subjects: 58 men (mean age 60.2 ± 12 years) and 285 women (mean age 53.4 ± 14.3 years). Interviews regarding information of tobacco smoking were conducted using the same questionnaire. To assess the relative risk of DTC logistic regression analysis adjusted to age was used.

Results: There was decreased risk of DTC among current smokers (OR = 0.61; 95% CI: 0.35–1.06) and increased in former smokers (OR = 1.60; 95% CI: 1.08–2.36). There was increased risk of DTC in smokers above 20 cigarettes per day (OR = 1.73; 95% CI: 0.57–5.28) and in smokers with age of initiation of smoking below 18 years of age (OR = 1.27; 95% CI: 0.67–2.40).

Conclusions: Current smoking seems not to be a risk factor of DTC. Increased risk of DTC in former smokers may result from coexistence of other factors and it needs further studies.

P7: Primary thyroid lymphoma, a rare thyroid disease with a good prognosis

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Background: Primary thyroid lymphoma is an uncommon tumour representing 1–5% of all thyroid malignancies.

The aim of the study was to review our experience and management of primary thyroid lymphoma and to discuss the diagnostic and therapeutic considerations.

Methods: Five women and one men with primary thyroid lymphoma were observed in our department from 1995. The clinical course and pathological spectrum of this disorder affecting the thyroid gland were reviewed.

Results: Clinical symptoms, including a rapidly enlarging painless neck mass, dysphagia and dyspnoea were present in all cases. Nodular goiter was observed in three patients, thyrotoxicosis and subclinical hypothyreosis in course of Hashimoto’s disease were observed in two cases at the time of diagnosis. Fine-needle aspiration cytology (FNAC) was performed in all patients. Initial diagnosis of thyroid lymphoma was established only in one patient.

Three patients were diagnosed as anaplastic or follicular thyroid carcinoma, in two cases FNAC was non diagnostic. All of the patients underwent an initial surgical procedure; in one case emergency debulking of the tumour in the course of acute airway obstruction with transient tracheostomy was performed. Five patients received combination chemotherapy with or without irradiation. A final diagnosis of thyroid B-cell non-Hodgkin’s lymphoma was confirmed in all these patients. Overall survival and disease free survival during follow-up was 100%.

Conclusion: The diagnosis of primary thyroid lymphoma should be considered when dealing with rapidly growing goiter. The role of FNAC is limited and surgical intervention is needed for a confirmatory diagnosis of thyroid lymphoma using combined histology and immunohistochemistry. A combination of chemotherapy and irradiation is the mainstay treatment which improves prognosis.

P8: Contribution of different genes in genetic predisposition to Graves’ disease (GD) — multiple logistic regression approach

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Objectives: The purpose of the study was to evaluate interactions between genes involved in development of GD, as well as an attempt to correlate different genotypes with specific phenotypes. An influence of possible genetic risk factors on GD disease was investigated based on the set of selected genes such as TNE, LTA, CTLA, HLA-DRB1-03, TG, CD40, IL-10, IL4, OAS, NFKB, LYP, RTSH.

Methods: The study population consisted of 1951 patients including 735 GD subjects. Due to the missing data a Bayesian approach has been applied followed by a multivariate logistic regression.

Results: Four genes were indicated as plausibly characteristic for GD in Polish population: TNE, CTLA, HLA-DRB1-03 and NFKB (the effect of remaining gene mutations was estimated as insignificant). In order to distinguish the genetic heterogeneity in the dataset, GD patients were divided into several subsets according to gender, age and age of onset of the disease. The presence of mutation in TNE, LTA and HLA genes, on the basis of OR value was related to the age of disease onset, while TG mutations may be responsible for female preponderance of GD.

Conclusions: The study allowed to initially select genes predisposing the subgroups of patients according to the age of onset of the disease — TNE, LTA and HLA genes and gender (TG genes). It constitutes an individual approach towards the patients with GD.
Grant No N519 579938

Table I. Logistic regression estimates of risk factors for GD

Gene	Mean (regr. coef.)	Stand. dev.	Cred. 95% int.	Odds ratio (OR = exp(coef.))	p-value
TNF	0.3321	0.1348	(0.0690–0.6002)	1.39	0.0074
CTLA	0.3813	0.0824	(0.2186–0.5430)	1.46	< 0.0001
HLA-DRB1-03	0.7117	0.1745	(0.3740–1.0520)	2.04	< 0.0001
NFKB	0.2980	0.0770	(0.1501–0.4473)	1.35	< 0.0001

P9:
Comparison of thyroid volume and goiter measured by means of ultrasonography and SPECT with use of 131I in smokers and non-smokers

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Introduction: The aim of the study was to estimate the volume of the goiter by means of US and 131I-SPECT and to estimate the influence of nicotine on thyroid volume according to patients' sex.

Material and methods: The study group contained 50 patients with goiter, where the volume of the thyroid was evaluated with use of US and 131I-SPECT. The control group contained 30 patients with normal volume of the thyroid gland shown by US and 131I-SPECT. The patients from the examined and control group were divided into two subgroups — smokers and non-smokers. US of the thyroid gland was made by means of an ALOKA SSD 500 device. SPECT was performed by means of a single-headed gamma camera by Diacam. **Results:** The average volume of thyroid gland measured by 131I-SPECT was significantly larger according to US in the examined and control group in smokers and non-smokers. We did not show statistically significant correlations between levels of iodine uptake and volumes of goiter evaluated by US examination together with 131I scintigraphy.

Conclusions: Significant differences in average values of thyroid volume between smokers and non-smokers were not observed, which might suggest a lack of goitrogenic activity of tobacco smoke or indicates a potential goitrogenic influence not significant enough in the examined group.

P10:
Thyroid hormone profile and NT-proBNP levels in the assessment of heart failure severity

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A low T3 syndrome was described in patients with heart failure (HF), and it appears to be associated with adverse outcome, representing an independent predictor of mortality. On the other hand, an elevation of brain natriuretic peptides (BNP and NT-proBNP) may represent a warning signal for future cardiovascular disease and may be an early marker of diastolic dysfunction. Arterial hypertension (AH) and diabetes mellitus type 2 (DM2) are known risk factors for the development of diastolic dysfunction and HF. The aim of our study was tested the hypothesis that impaired levels of thyroid hormone profile (especially FT3 and rT3) assessed together with NT-proBNP are better predictive marker than assessed separately. Assessment of these two parameters could be sufficient to determine asymptomatic cardiac impairment.

Fifty patients were qualified to our study (17 with HF — group I, 17 with DM2 and AH — group II and 16 healthy volunteers). In each patient thyroid hormone profile (TSH, FT4, FT3 and rT3) and NT-proBNP were assessed.

Echocardiography was performed according to the Polish Cardiac Society standards. Radioisotope ventriculography was performed with using gamma camera E.CAM 180 (Siemens).

No statistically significant differences in TSH and FT4 between groups were observed. FT3 was lowest in group I ($p < 0.05$) and negative correlation with NT-proBNP ($R = -0.47$, $p < 0.05$) and positive with ejection fraction (EF) of the left ventricle ($R = 0.25$, $p < 0.05$) were observed. FT3 in group II also was lower than in control group but results were not statistically significant. Systolic heart failure with low ejection fraction (EF) was observed in all patients in the group I. Diastolic heart failure with E/A index below 1, but in two patients with higher E/E' index and left atrium enlargement, was observed in the group II.

Results were confirmed in radioisotope ventriculography. No changes in systolic and diastolic function were observed in the control group. Results of rT3 are currently under development.

Assessment of thyroid hormone levels in the patients with HF could give more information about severity of the disorder. Echocardiography or radioisotope ventriculography should be performed in the patients with AH and DM2 for searching cardiac diastolic dysfunction.

P11:
The patient with adrenal insufficiency and Graves-Basedow's disease

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A 42-year-old patient was admitted to the Department in April 2011 in severe general condition due to hipermetabolic crisis. The patient had no previous medical history of any endocrine disease. Over the previous few weeks he had lost about 10 kg of weight and had observed growing weakness, nausea, vomiting, abdominal pain and darkening of the skin. On the surgical ward he had been diagnosed for suspected ulcer disease. In laboratory tests, which were performed at admission we observed TSH < 0.0025 uU/ml, fT4 2.11 ng/dl, fT3 2.46 pg/ml, TRAb 3.44 IU/l and features of autoimmune thyroid disease in US examination. At the time of admission we also assessed ACTH level — 672.9 pg/ml and cortisol — 4.00 μ g/dl. Patient was diagnosed with both: hipermetabolic and adrenal crisis. Initially he was treated with intravenous thiamazole (80 mg per day) and dexamethasone (16 mg per day) with rapid improvement of his general condition. In the long term treatment thiamazole (20 mg per day), hydrocortisone (40 mg per day), and fludrocortisone (0.1 mg per day) were used.

Coexistence of Addison's disease with Graves' disease is observed in 13% of patients with adrenal insufficiency. The vast majority of them are women. The combination of these diseases is part of the type 2 autoimmune polyglandular syndrome. The coexistence of exacerbation of both conditions: adrenal insufficiency and Graves' disease is rare.

P12:
A difficult diagnosis: a case report of combined Riedel's disease and fibrosing Hashimoto's thyroiditis

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The authors report a case of a female patient displaying clinical, laboratory and radiological traits of Riedel's thyroiditis and Hashimoto's disease.

Patient Findings: A 44-year-old Caucasian female was diagnosed with hypothyroidism. A fine-needle aspiration biopsy was performed; findings were suggestive of an exacerbated chronic inflammatory process, however a small lymphocyte-derived malignancy could not be ruled out with certainty; the patient was referred for elective thyroidectomy. The microscopic features of specimens did not meet the criteria of Hashimoto's thyroiditis. The immunohistochemical studies revealed few scattered B lymphocytes (CD20 positive) and numerous scattered T lymphocytes (CD3 positive). Finally, Riedel's thyroiditis with an intense inflammatory infiltrate composed of lymphocytes was diagnosed.

Summary: Reaching a diagnosis was particularly difficult in this patient, since Riedel's thyroiditis, the fibrosing form of Hashimoto's disease and malignant tumors of the thyroid can show similar traits upon physical and histopathological examination. As the clinical data were indicative of Hashimoto's thyroiditis and there were partial histological criteria of two forms of thyroiditis, namely Hashimoto's and Riedel's, the very rare diagnosis of a combined disease was made. Dense B and T lymphocytes and some plasma cell infiltrates, as well as the destruction of thyroid follicles by fibrosis extending into surrounding tissues were supportive of the final diagnosis.

Conclusions: Differentiating between the histopathological and clinical presentation of both of the diseases in one patient is difficult, primarily due to the partial overlapping of their histopathological traits. In order to avoid a diagnostic error, a close cooperation between the endocrinologist and pathologist is mandatory. It is the authors' opinion that in our patient the two diseases existed separately, and their coexistence was most likely coincidental.

P13: Influence of radioiodine treatment on thyroid volume in patients with subclinical hyperthyroidism

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Introduction: Subclinical hyperthyroidism (SH) concerns about 1% of population. The treatment of choice of SH is radioiodine, when its reason is thyroid autonomy.

Aim: Assessment of influence of treatment with ¹³¹I on thyroid volume in patients with subclinical hyperthyroidism.

Material and methods: 44 patients (37 women and 7 men) at age 45.9 ± 11 with over one year history of autonomous SH were included to the study. Among them: 38 (86.4%) with multinodular goiter, three (6.8%) with parenchymal goiter and two (4.5%) with single nodule goiter. Thyroid volume was assessed by ultrasound examinations which were performed twice: before and 5.7 ± 4.2 months after TSH normalization due to ¹³¹I treatment in dose 12.1 ± 5.7 mCi. Radioiodine uptake after 24 hours was $30 \pm 15\%$. The local ethical committee approval has been obtained earlier.

Results: Radioiodine treatment patients with SH caused 30% decrease of thyroid volume (from 33 to 22 ml — $p < 0.001$).

Conclusion: Treatment with radioiodine of patients with autonomous subclinical hyperthyroidism causes 30% decrease of thyroid volume after half a year.

P14: Thyroid function and iodine supply in the group of healthy pregnant patients from Mazovia — preliminary data

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Key words: pregnancy, iodine, thyroid.

Thyroid dysfunction in pregnant woman can negatively affect fetal development and pregnancy course. Iodine deficit has important influence on thyroid function. Influence of physiological pregnancy on parameters of thyroid function makes interpretation of laboratory tests of thyroid function difficult.

Aim: Prospective observation of thyroid function and iodine intake in healthy pregnant women supplemented with 150 µg of iodine daily.

Methods: Assessment of thyroid function: concentration of TSH, free thyroid hormones, morning urinary iodine in consecutive trimesters of pregnancy.

Study group: 40 pregnant women (age 24–36 y, mean 29). Single pregnancies, resulting in birth of healthy neonates.

Results: TSH concentrations were within values recommended for pregnancy and were: mean 1.27; 1.92 and 1.73; median 1.38; 1.92 and 1.51 IU/l respectively in the following trimesters of pregnancy. Free T4 was within pregnancy reference values and decreased in the III trimester, mean concentrations were 1.26; 1.0; 0.99 ng/dl in subsequent trimesters. Urinary iodine concentrations (UIC) were unexpectedly low at the beginning of pregnancy: mean 98 µg/l, median 89 µg/l and in 62% of the subjects were lower than 100 µg/l. In spite of supplementation with at least 150 µg iodine per day, mean UIC were respectively 133 µg/l and 140 µg/l; median 122 µg/l and 129 µg/l in the second and third trimester.

Conclusions: Observations are preliminary: 1. TSH and free T4 values did not exceed population reference values, dynamics during pregnancy was as expected. 2. Low urinary iodine concentration at the beginning of pregnancy and during supplementation reveals that recommended prophylaxis does not ensure sufficient iodine supply in the group of pregnant women.

P15: The frequency of appearance of autoimmunological inflammation of thyroid in patients with protracted hepatitis treated with interferon

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Introduction: Current methods of treating infectious hepatitis are linked to usage of interferon and ribavirin. When treated with interferon side effects appear like thyroid diseases.

Objectives: The frequency of appearance of autoimmunological inflammation of thyroid in patients with protracted hepatitis treated with interferon.

Methods: The research was participated by 149 people with protracted hepatic type B and C, aged 18 to 70: average 43.9 years

\pm 12.87. Patients before treatment, after 6 and 12 months of treatment density of serum was assessed in: thyroid stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (FT3), thyroglobulin (Tg), antithyroid antibodies: thyroid peroxidase antibodies (ATPO) and thyroglobulin antibodies (ATG). Additionally the echostructure of thyroid USG was assessed. Patients with thyroid dysfunctions had the used interferon compliance. 24 patients were diagnosed with AZT when 12 were treated with pegylated interferon and 12 with recombinant interferon. Among all 149 patients 60 were given pegylated interferon and 89 recombinant interferon.

Results: Research on patients with protracted hepatitis before treatment with interferon found 9 of them (6.04%) with increased density of antithyroid antibodies. In this group 6 were in euthyroid (during treatment 4 patients appeared to have underactive thyroid, 1 overactive thyroid and 1 with changing thyroid functions first overactive and then underactive) and another 3 patients with hypothyroidism (during treatment 2 patients maintained underactive thyroid and 1 appeared to have euthyroid). 24 patients (17.14%) on interferon treatment who firstly did not show any features of auto-immunological process, were diagnosed with increased antithyroid antibodies. The average results for ATPO before and after 6 and 12 months were: 12.4, 310.4, 141.3 IU/ml. For ATG: 17.40, 108.0, 125.6 IU/ml. In this group of patients after 3 months of treatment 3 got overactive thyroid, and 1 underactive thyroid, after 6 months 11 were diagnosed with overactive thyroid and 6 with underactive thyroid. After 12 months: 4 patients with overactive thyroid and 1 new diagnosed, 1 with change from hypothyroidism to hyperthyroidism, 2 continued with overactive thyroid, 4 with hypothyroidism and rest in condition of euthyroid. Whole group before treatment on USG showed decreased echogenicity of thyroid gland on 14.7%, after 6 months 18% and after 12 months 22.5%.

Findings: Patients treated with interferon because of protracted infectious hepatitis are in risk of progress of new or strength of existing autoimmunological inflammation of thyroid. Kinds of used interferon do not show relationships with thyroid gland disorders.

P16:

Resistance to thyroid hormone syndrome in four patients

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Introduction: Resistance to thyroid hormone is the syndrome (RTHS) with variable degree of tissue hyposensitivity to thyroid hormones. Patients with RTHS have elevated FT4 and FT3 with non suppressed TSH. Traditionally syndrome is classified as generalized, pituitary or peripheral type.

The aim was presentation of the RTHS clinical picture and the impact of concomitant thyroid diseases on its course in our material. **Material:** 3 females and one male aged 47–62, hospitalized in 2006–2011.

Methods. Clinical picture and diagnostic procedures needed for confirmation of thyroid disorders have been performed.

Results: Female 58, with cardiologic disorders, suspected of amiodarone-induced thyrotoxicosis. In the past, she was treated many times with antithyroid drugs because of elevated thyroid

hormones. Small goiter. FT4 38.5 pmol/L, FT3 8.6 pmol/l, TSH 4.63 IU/l. TSH after TRH = 19.27 IU/l. MRI excluded pituitary adenoma. Clinically euthyroid. **Male 62**, with bilateral forearm fracture. Normal thyroid size. Before surgery, in routine thyroid hormone evaluation: FT4 24.4 pmol/l, FT3 7.4 pmol/l, TSH 2.14 IU/l. TSH after TRH = 7.65 IU/l. Clinically euthyroid. **Female 59**, in the past subtotal thyroidectomy because of toxic nodular goiter. Hospitalized with the symptoms of severe hypothyroidism after thyreostatics due to recurrent hyperthyroidism, with concomitant normal FT4 and FT3 concentrations and TSH > 77.9 IU/l. After cessation of the antithyroid therapy, hyperthyroidism recurred with FT4 — 29.1 pmol/l, FT3 — 5.8 pmol/l. TSH 24.9 IU/l. TSH after TRH = 58.13 IU/l. MR imaging revealed normal pituitary. **Female 47**, with the symptoms of hyperthyroidism. After pharmacological treatment clinically euthyroid with FT4.44 pmol/l, FT3 5.8 pmol/l, TSH 1.8 IU/l. TSH after TRH = 9.5 IU/l. High levels of TSI and TPO autoantibody, confirmed concomitant autoimmune thyroid disease. Normal pituitary MR imaging.

Conclusions: RTHS is characterized by large heterogeneity of clinical picture. Coexisting thyroid disorders complicate its course and can cause diagnostic difficulties.

P17:

Thyroid disorders in women with Turner's syndrome — own observations

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Introduction: Thyroid disorders including Hashimoto's thyroiditis tend to be observed more frequently in women with Turner's syndrome. Hypothyroidism is reported in 16–87.5% of those patients and hyperthyroidism only in 2.5%. In women with Turner's syndrome, as well as in the general population, the frequency of thyroid abnormalities increases with age. There is no difference in the incidence of thyroid dysfunction related to the form of karyotype abnormality.

The **aim of study** was to evaluate the frequency, etiology and forms of thyroid pathology in group of adult women with Turner's syndrome treated in our clinic.

The **study group** included 11 females aged 23 to 72 years. The diagnosis of Turner's syndrome was based on the clinical picture and a karyotype test.

Methods: The patients were screened for thyroid abnormalities by clinical evaluation and laboratory examination. The laboratory assessment included thyroid structure (USG), thyroid function (TSH, FT4, FT3) and antithyroid antibodies. The tests were performed using standard hospital laboratory procedures.

Results: Thyroid pathology was detected in 9 cases (82%). Chronic lymphocytic thyroiditis was diagnosed in seven female patients with hypothyroidism (63.7%) and Graves' disease was found in one patient with hyperthyroidism. Normal thyroid function was confirmed in one patient with an elevated level of anti-TPO antibodies and in another one with nodular goitre in an ultrasound examination.

Conclusion: 1. Thyroid pathology is the most frequent form of endocrinological disorders in patients with Turner's syndrome. 2. Hashimoto's thyroiditis and hypothyroidism are the most prevalent types of thyroid disorders in women with Turner's syndrome.