APPENDIX

Poznan University
of Medical Sciences
Poland

27th Bilateral Symposium Poznan-Halle

Rare diseases in clinical practice

15th–17th of December 2017

As part of long-term bilateral cooperation with Martin Luther University in Halle, the 27th Bilateral Symposium Poznań-Halle "Rare diseases in clinical practice" was held on December 16. The participants of the symposium included research workers of both partner universities. On this occasion, talks were held to set up research groups that will carry out joint activities in the field of science and research and the first Poznań-Halle groups were tentatively established. Presentation of prizes for the best oral and poster presentations is a long-standing tradition of the symposium. This award is named after two Professors: Prof. Zeige and Prof. Hasik, who initiated cooperation between our Universities over 30 years ago. In the current edition of the symposium the first prize, two second prizes and two third prizes were given. To add, two representatives of our university were honored. The first prize went to Krzysztof Piersiała, a 6th year student of the First Medical Faculty I and the deputy chairman of the Student Scientific Club at the Clinic of Otolaryngology and Laryngological Oncology. The awarded work was written under the supervison of Prof. Małgorzata Wierzbicka, who is the Head of the Clinic and Joanna Jackowska M.D., Ph.D. The third prize went to Dr Michał Prendecki, who is preparing a doctoral dissertation at PUMS Department and Clinic of Neurology (Head: Prof. Wojciech Kozubski). The work presented at the symposium was prepared in the Laboratory of Neurobiology and supervised by Prof. Jolanta Dorszewska, who tutors Dr Prendecki's doctoral thesis.

Heart amyloidosis in the clinical practice

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One of the rare conditions that cause heart hypertrophy is amyloidosis. Pathomechanism of this disease results from extracellular tissue deposition of insoluble fibrils composed of serum proteins — amyloid. There are many types of amyloid precursors: light chain immunoglobulin, transthyretin- mutant hereditary or wild-type, serum amyloid A protein. The organs typically involved are liver, kidney, gastrointestinal tract or heart. The extent of heart involvement differs with the type of amyloid. To properly manage and treat patients with heart amyloidosis it is essential to know the type of amyloid. The first step in the management of this disease is a demonstration of amyloid deposition in the tissue biopsy- fat pad, heart, mucosa and it's staining with red Congo to prove amyloid deposits. Then one needs to characterize the type of amyloid, and it is done with immunohistochemical reactions. Unfortunately, in our clinical practice, we lack proper tissue characterization. Since this step is indispensable in differential diagnosis between various types of amyloid, resulting in different ways of treatment- for example, chemotherapy in light chain amyloidosis, liver transplant in transthyretin type, it is of great importance for our cardiology department to develop cooperation with histopathological department/laboratory familiar with amyloidosis diagnostics.

The main points of collaboration:

- Collaboration in the diagnostic procedures, especially in pathomorphological or laboratory tests
- Collaboration in the development of the heart amyloidosis registry
- Collaboration in the exchanging practical/clinical experience during mutual visiting possibilities.

Vitamin K status in patients after restorative proctocolectomy

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ABSTRACT

Aim. Fat-soluble vitamins such as vitamin K are inevitably associated with large intestine physiology. Surgical resection of the entire colon allows assuming significant vitamin K malabsorption in patients after restorative proctocolectomy (RPC). The objective of the study is to evaluate vitamin K status in patients after RPC.

Material and Methods. The study comprised of 49 patients operated due to ulcerative colitis (32; 17 women, 15 men) and familial adenomatous polyposis (17; 8 women 9 men). The vitamin K status has been assessed by the concentration of uncarboxylated prothrombin (PIVKA-II) measured with the use of enzyme-linked immunosorbent assay.

Results. Elevated PIVKA-II levels (≥ 2 ng/ml) occurred in 57.1% of patients studied. Spearman correlation coefficient analysis showed a moderate correlation between PIVKA-II levels and PDAI as well as chronic inflammation (respectively 0.498 and 0.491; $p < 0.05$). We observed a weak correlation between PIVKA-II levels and Moskowitz scale (0.352, $p < 0.05$), ESR (0.372, $p < 0.05$), albumin (-0.324; $p < 0.05$) and CRP levels (0.312; $p < 0.05$). No differences have been shown in PIVKA-II levels depending on the time from operative treatment, sex, the presence of adenomatous polyps in the pouch, INR value, and the hemoglobin level.

Conclusions. Vitamin K deficiency is frequent in subjects after RPC presented. However, none of the patients had its overt manifestation such as bleeding.

Oral health status in patients with mucopolysaccharidoses — exemplary cases

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Introduction. Mucopolysaccharidoses (MS) is a group of inherited lysosomal storage disorders characterized by the defective activity of lysosomal enzymes. The excessive accumulation of uncleaved mucopolysaccharides results in progressive cellular damage, organ malfunction and skeletal abnormalities. Patients with MS often suffer from physical and mental disabilities, which together with poor access to professional dental care may lead to impaired oral health.
Aim. To assess the oral health status and the properties of the saliva in patients with MS.
Material and Methods. Thirty individuals with MS were examined. They were recruited from The Society for Mucopolysaccharidoses and Rare Diseases (SMRD) registry and represented all types of MS found in Poland. The teeth were assessed as is, i.e. without prior drying and/or cleaning. When possible, unstimulated whole mixed saliva was collected and analyzed for inflammatory mediators and antioxidant status by colorimetric and immunoassays. The results were compared with those recorded in age- and sex-matched healthy controls undergoing routine dental examination.
Results. The group of MS patients displayed significant heterogeneity in terms of demographic criteria, staging of the disease, the presence of mental retardation, the degree of disability and oral health status. It was clear, however, that on the whole, they suffered from the markedly higher prevalence of caries, inferior gingival status, and poor oral hygiene. In this respect, exemplary cases are present to highlight typical problems in oral health found in patients with MS. Moreover, the samples of saliva could be collected only from 4 less handicapped individuals and exhibited a large scatter of values. The only possible tendency observed was that of the decreased salivary concentration of VEGF (139 ± 68 vs. 313 ± 184 pg/ml).
Conclusions. Patients with MS suffer from poor dental and gingival status, and inadequate oral hygiene. The severity of these problems is generally proportional to the degree of disability associated. Thus, patients rare diseases as exemplified by MS constitute a population with special needs in terms of oral health and require a coordinated oral care.

Mutations of the *DIAPH2* gene in head and neck cancer are overrepresented in metastasizing tumors and result in a shift from "proliferation" to "migration" cellular phenotype

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Previously we have screened laryngeal squamous cell carcinoma (LSCC) cell lines using high reso-

lution array-CGH in order to delineate novel tumor suppressors inactivated during cancer progression. Within the identified bi-allelic-losses we found a hemizygous deletion of the X chromosome located *DIAPH2* gene. The encoded protein belongs to a highly conserved formin family sharing the FH (formin homology) domain crucial for actin polymerization. In line with this function, literature suggest an involvement of these proteins in regulation of cell movement and adhesion and therefore point to *DIAPH2* as to a novel candidate for a metastasis related gene.

Intrigued by the interesting biological function of the encoded protein, as a proof of principle, we sequenced the gene in 5 LSCC metastases-derived cell lines assuming the highest probability to identify further loss of function alterations in these samples. Indeed, we identified a hemizygous deletion targeting *DIAPH2* in 1/5 cell lines.

These preliminary findings triggered us to sequence the entire coding region of the gene in 95 primary LSCC specimens (Illumina MiSeq; paired-end sequencing, coverage: range 20–6451, median 528) that included 53 non-metastasizing (N0) and 42 metastasizing (N+) tumors. We aimed at identifying further loss-of-function mutations and their distribution in these two groups. Moreover, we combined our results with exome sequencing data from 279 head and neck tumors available in the cBioPortal. Altogether 21 mutations (5.6%) were found in the 374 studied cases that targeted functional domains of the DIAPH2 protein, wherefrom 6/190 were N0 cases and 15/184 were N+ cases. Importantly, there was a significant overrepresentation of the mutations in the (N+) cases ($p = 0.036$; chi-squared test).

In order to analyze the biological effect of these mutations we used CRISPR/Cas9 editing to delete six amino acids form the crucial FH3 domain and to establish the *DIAPH2*$^{+/-}$ HEK-293 cell line. Subsequent proliferation and migration assays proved that this heterozygous loss significantly alters the behavior of cells that slow down their proliferation but manifest enhanced migration.

In conclusion, these findings show the overrepresentation of *DIAPH2* mutations in metastasizing tumors. Moreover, the increased migration potential of *DIAPH2*$^{+/-}$ cells suggest that these mutations may contribute to metastasis formation in human tumors.

Immunophenotypic assessment of Natural Killer cells in Chronic Rhinosinusitis with Nasal Polyps

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Introduction. Chronic rhinosinusitis is a chronic inflammatory process of the mucous membrane of the nasal cavity and paranasal sinuses. In the physiological state NK cells are the first line of defense against pathogens leading to cytolysis of the infected cell. However, this function may be limited under pathological conditions.

Aim. The aim of the study was to evaluate percentage and the degree of maturation of NK cells and also expression of CD314, CD336, CD337 receptors in peripheral blood and tissue from patients with chronic sinusitis with and without polyps as well as from healthy people.

Material and Methods. The research material was obtained from 49 patients with chronic sinusitis (36 with nasal polyps, 13 without polyps) undergoing endoscopic nasal and sinus surgery and also from 15 patients with nasal septum deviation and hypertrophic rhinitis as control samples. Immunophenotypic identification of NK cells was carried out with the use of flow cytometer.

Results. The results did not show any significant differences in the percentage of NK cells in the analyzed groups. Significant differences were present within the degree of maturation of NK cells between the examined groups and tissues. In the material from patients with chronic sinusitis lowered expression of the receptors has been found compared to the control group. The results indicate the involvement of NK cells in inflammation process, and the different expression of receptors in the analyzed groups may indicate the presence of a modifying agent.

Conclusions. Disorders of the maturation process and lower expression of receptors activating function of NK cells may be an important element of etiopathogenesis of chronic rhinosinusitis with and without polyps.

Systemic and oral symptoms as well as dental management in the Hyperimmunoglobulin E syndrome patients — report of two cases

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The autosomal dominant hyperimmunoglobulin E syndrome (HIES) due to a loss-of-function heterozygous transcription factor STAT3 mutation is a multisystem disease with immunological and non-immunological abnormalities. The syndrome is characterized by a classical triad of symptoms, such as eczema, recurrent respiratory tract infections and high serum concentration of IgE, which is accompanied by a variety of oral, dental, skeletal, connective tissue, vascular and dysmorphic features. As clinical manifestations of the disease often appear gradually, the clinical diagnosis of HIES in early childhood is challenging. The oral findings manifest earlier than the development of typical facial changes, hence, the expected role of oral phenotypes in early diagnosis of the disorder exist. The dermatological symptoms, oral status, other systemic health problems as well as dental management of two paediatric patients with hyperimmunoglobulin E syndrome were presented. HIES is of great importance to different health care providers because sufferers require special preventive and therapeutic management from early infancy in order to avoid complications which can even prove to be life-saving for such patients.

Identification of single nucleotide polymorphisms, rs396991 of the *CD16A* gene and rs1801274 of the *CD32A* gene, as possible factors influencing bullous pemphigoid and pemphigus phenotypes

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IgG Fc receptors (FcRs) may be important immunomodulatory factors participating in the pathogenesis of bullous pemphigoid (BP) and pemphigus. The aim of the study was to identify and evaluate the possible association between the expression of certain single nucleotide polymorphisms (SNP) of *CD16A* and *CD32A* genes and the disease phenotype. This study was focused on rs396991 of the *CD16A* gene and rs1801274 of the *CD32A* gene in pemphigus and BP.

The study comprised 47 patients with BP and 15 patients with pemphigus serving as mutually positive control groups. DNA was isolated from whole blood by column methods and analysed using a NanoDrop spectrophotometer. Genotyping was performed with the use of TaqMan SNP Genotyping Assays (ThermoFisher) and a LightCycler 2.0 real-time PCR instrument.

The frequency distribution of SNP genotypes for *CD16A* gene was as follows: (i) in BP: 21 (44.68%) homozygotes AA, 22 (46.80%) heterozygotes CA, 4 (8.52%) homozygotes CC; (ii) in pemphigus: 5 (33.33%) homozygotes AA; 8 (53.34%) heterozygotes CA, 2 (13.33%) homozygotes CC.

The frequency distribution of SNP genotypes for *CD32A* gene was as follows: (i) in BP: 9 (19.15%) homozygotes TT, 5 (53.19%) heterozygotes TC, 13 (27.66%) homozygotes CC; (ii) in pemphigus: 4 (26.66%) homozygotes TT; 8 (53.34%) heterozygotes TC, 3 (20%) homozygotes CC.

These polymorphisms may play a significant role in the pathogenesis of BP and pemphigus influencing their dynamic phenotypes.

The patient with distal arthrogryposis and with labia minora hypertrophy-medical and ethical aspects

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Freeman–Sheldon syndrome (FSS), also termed distal arthrogryposis type 2A (DA2A), or Whistling-face syndrome, was originally described by EA Freeman and JH Sheldon in 1938. The symptoms of Freeman–Sheldon syndrome include drooping of the upper eyelids, strabismus, low-set ears, a long philtrum, gradual hearing loss, scoliosis, and walking difficulties. Gastroesophageal reflux has been noted during infancy, but usually improves with age. The tongue may be small, and the limited movement of the soft palate may cause nasal speech. Often there is an H- or Y-shaped dimpling of the skin over the chin. We described a case of a labioplasty in 18 years old patient with FSS and labia minora hypertrophy which is to our knowledge first reported case of coincidence of FSS with genital abnormalities. Ouer Patient was diagnosed with Freeman-Sheldon syndrome in an early childhood and since then she passed several reconstructive surgeries and rehabilitation. At the admission ouer patient reported discomfort, pain and physical activity limitation due to labia minora hypertrophy and hyperpigmentation. Patient was informed about the possibility of labioplasty procedure, accepted the proposal of surgical treatment and signed the informed consent. Labial reduction was performed by the wedge resection of labia adjusting the size to the desired one (2 cm length between the base and the wedge). Three weeks and six months after surgery the patient reported full acceptance of her genital anatomy. She did not mention any more the hyperpigmentation of labia and reported successful sexual life with her boyfriend. Incorrect and unacceptable genital anatomy in adolescents might lead to severe sexual dysfunctions. From the ethical point of view it is fully understandable and permissible to conduct reconstruction surgery after injuries and in illnesses, or to repair deformations stemming from congenial malfunctions. In some cases it may be even considered necessary or indispensable to undergo plastic surgery. This is particularly true for children with malfunctions which may in the future stop their personal development. In such situations the burden to recognize the necessity and to take action lies with the parents.

Labioplasty in a FSS patient with labia minora hypertrophy can help to obtain both the full acceptance of genital anatomy and successful sexual life. To our knowledge this is a first report of labia minora hypertrophy in a patient with FSS. As far no embryological connection between the labia minora overgrowth and Freeman-Sheldon syndrome was reported.

Isolated hypogonadotropic hypogonadism in clinical practice

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Department of Endocrinology, Metabolism and Internal Medicine of Poznan University of Medical Science since many years conducts research on isolated hypogonadotropic hypogonadism (IHH). A result of these studies is collection of unique cohort patients presenting IHH, which also includes the familial cases. IHH is a significant cause of disorders of maturation and infertility in human. IHH is five times more common in males than in females. GnRH neuronal migration disorders and defects in the synthesis, secretion and

action of gonadotropin releasing hormone (GnRH), luteinizing hormone (LH) or follicle-stimulating hormone (FSH) underlie the background of IHH. IHH is divided into two types: a type with anosmia (lack of smell), called Kallmann syndrome and normosmic form (without disturbances of smell) — nIHH. Kallmann syndrome accounts for about 60% of IHH. IHH patients can have accompanying defects such as renal agenesis, deafness, cleft palate, mirror movements or digital anomalies etc.

To date, more than 25 genes involved in the pathogenesis of IHH have been identified. However, the genetic basis of approximately half of the IHH cases remains unidentified. The next generation sequencing (NGS) with use of platforms of high- or medium-throughput represents nowadays most advanced and efficient tool for identification of genetic background of IHH.

Reversal of IHH, observed in 10% of IHH patients, is defined as reinstatement of normal testosterone concentration in serum after short discontinuation of treatment with testosterone, gonadotropin or GnRH. Mutations in FGFR1, PROKR2, KAL1, GNRHR, TACR3, TAC3 were identified in several cases of reversal.

The knowledge of genetic background of IHH helps to individualize the treatment and help to predict reversion of hypogonadism. Early appropriate clinical and genetic diagnostics and treatment are crucial for achieving optimal clinical results and effective counseling.

Oral health status and tobacco smoking as a risk factor for stroke

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Aim. We analyzed the oral health status and periodontal status of post-stroke patients from Clinic of Vascular Diseases of Nervous System to assess a possible link between stroke and severe periodontitis.

Material and Methods. Data has been provided between 2014–2017. Within 72 hours post stroke each patient has been examined by staff from Periodontology Clinic. The periodontal state of all participants was assessed according to the WHO Oral Health Data Chart and the following indices: API, BOP,CAL,PD. The control group, the same age and sex, has been taken from a group of Periodontal Clinic Patients. The group consist of 240 patients,128 women and 112 mean age 43–92 years with chronic periodontitis (96) and gingivitis(82).About 20% was edentulous.

Results. We found significant difference in the BOP and API values between the two groups analyzed: the post stroke patients smoking and no smoking and the healthy controls. Our preliminary data suggest that periodontal disease may be a factor predisposing to stroke.

Conclusions. Emerging evidence suggest that poor oral health control influences the initiation and/or progression of atherosclerosis (including infarct and stroke). We found significant differences in the BOP and API values between patients and control subjects which confirm that periodontitis can be predisposing factor to stroke.

Analysis of genotype-phenotype risk factors in families with history of Alzheimer's disease

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Introduction. Currently, 50% of cases of rare, familial form of Alzheimer's disease (AD), is connected with mutations in three genes associated

with amyloid β (Aβ) cascade: *APP*, *PSEN1* and *PSEN2*. The causative factors for remaining cases of familial AD (FAD) have not been fully elucidated. The aggregation of unfavorable variants in *APOE* — responsible for diminished Aβ clearance and *TOMM40* — associated with Aβ transfer to mitochondria, and increased oxidative stress, may induce development of AD in certain families. The *APOE* possesses three common variants: protective — E2, neutral — E3 and pathogenic — E4. Simultaneously, the *TOMM40* rs10524523 polymorphism comprise following alleles: short (S), long (L) and very long (VL). These variants may influence the levels of biochemical parameters, such as: the protective apolipoprotein E (apoE), antioxidants, e.g. glutathione (GSH), and other biothiols, such as vasculature damaging homocysteine (Hcy). So far, very few studies were focused on investigation of the effects of genotype-phenotype risk factors for AD in subjects with family history of AD.

Aim. The aim of the study was the analysis of the genetic variants of *APOE* and *TOMM40* genes and the apoE phenotype, as well as the level of chosen biothiols in families with history of AD.

Material and Methods. The members of two families with history of AD and no detected mutations in hotspot regions of *APP*, *PSEN1* and *PSEN2* genes were recruited to the study. The variants in *APOE* gene were analyzed by qPCR, *TOMM40* by HRM and capillary electrophoresis while *APP, PSEN1, PSEN2* by sequencing. The plasma level of apoE was analyzed by ELISA. The concentrations of Hcy and GSH were analyzed by HPLC/EC.

Results. It was shown that in the analyzed families, the disease manifested about 65 years of age. All studied persons were carriers of at least one *APOE* E4 allele. Moreover AD patients, from studied families were carriers of unfavorable variants: *TOMM40* S and L, and exhibited elevated levels of Hcy and decreased concentration of apoE. Moreover, the presence of two *APOE* E4 alleles was accompanied with decreased apoE levels, both in AD patients and family members without signs of dementia.

Conclusions. It seems that the *APOE* E4 and *TOMM40* S/L alleles leading to the altered plasma concentrations of apoE and biothiols may increase the risk of developing AD in families with history of this disease.

Is trivial otitis externa always harmless?

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Introduction. Otitis externa is an infection of the outer ear canal with or without eardrum involvement. It is thought to affect 10% of people at some stage. In predisposed patients, this common disease may develop into life-threatening process which invades the temporal bone and skull base.

Material and Methods. Medical records in patients with MOE hospitalized in Department of Otolaryngology and Laryngological Oncology in Poznań between 2008–2017 was retrospectively analyzed. We review latest literature using the search terms: „malignant otitis externa", „skull base osteomyelitis".

Results. Analysis of medical records reveals that MOE affects more often elderly person over 70 years. There is sex predilection for men. Patients with DM, immune deficiency or with other systemic conditions develop predominantly MOE. Symptoms are frequently underestimated by patients and diagnostics is delayed. Currently, attempts have been made to unify terminology, diagnostics and treatment of temporal bone destructive processes in patient with MOE.

Conclusions. *Nonetheless, we should* also *bear in mind* that even trivial otitis externa may develop into the life-threatening disease. Multicenter study and metaanalysis are aimed to reach the consensus for the diagnosis, treatment and nomenclature of inflammatory processes invading temporal bone. In patients with MOE, prompt diagnosis and *sufficiently long* antibiotic treatment is required to provide better outcomes and avoid surgical approach.

Recessive dystrophic epidermolysis bullosa in the dental practice — description of two cases

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Epidermolysis bullosa dystrophica or dystrophic epidermolysis bullosa (DEB) is a genetically determined (autosomal dominant or recessive) disease characterized by the appearance of severe blistering lesions affecting skin and mucous membranes. DEB is caused by genetic defects within the human COL7A1 gene encoding collagen VII. The deficiency in anchoring fibrils impairs the adherence between the epidermis and the underlying dermis.

The aim of the study was to present two patients with recessive type of DEB also known as "Hallopeau–Siemens variant of epidermolysis bullosa", who are currently patients of the Department of Pediatric Dentistry of Poznan University of Medical Sciences.

The 12-year-old girl and her 9-year-old sister were referred to the university clinic seeking advice and treatment, due to rapidly progressing dental caries. Most of the teeth in both sisters presented with advanced caries demineralization demanding urgent dental intervention.

Dental caries lesions have been treated in local anesthesia, while extractions of posterior permanent teeth have been planned to be carried out under general anesthesia. Patients with DEB present a challenge for dental care, since every manipulation in oral cavity may result in blistering. At the same time, elimination of pain and discomfort due to caries is essential in improving the quality of life of the patients.

The blue light in examination of mucosa — the role of NBI in diagnostics

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Introduction. The present review is focused on the use of NBI in the diagnostic and management process of patients with laryngeal cancer. Narrow band imaging (NBI) by enhancing the contrast between the mucosal epithelium and submucosal vessels facilitates diagnosis of precancerous and cancerous lesions, as well as hypertrophic lesions such as laryngeal papillomatosis. Narrow band imaging (NBI) is an optical technique based on the modification of white light by the use of special optical filters. Every change in the microvascular architecture of the mucosa is classified according to Ni's classification (2011).
Material and Methods. The use and diagnostic efficacy of different optical diagnostic methods used in detection of larynx malignancies was studied based on a combined analysis of publically accessible databases (PubMed, MEDLINE, Cochrane Library) as well as experiences of *Department of Otolaryngology* - Head and Neck Surgery of *Poznan* University of Medical Sciences.
Conclusions. There is a wide range of evidence in the literature and in experience of our department that optical diagnostic methods such as NBI proved to be superior to white light endoscopy for the detection of early stages of larynx malignancies and thus have the potential to revolutionize early diagnosis of the larynx cancer. In addition, the use of NBI allows more precise assessment of the surgical margins status of early stage and locally advanced laryngeal cancers managed in endoscopic laser cordectomy.

What is the significance of Borrelia burgdorferi infection in morphea? Case report and literature review

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Morphea and lichen sclerosus are diseases of unknown etiology, however they are considered to have autoimmune Introduction. Their hypothetical association with Borrelia burgdorferi infection has been a subject to debate for a long time. 50-year-old male presented with a 5-month history of dermatosis. The patient rapidly developed multiple disseminated purple macules and pale indurations with liliac ring on the trunk and extremities. The patient has been working in the forest and reported multiple tick bites over last few years. He didn't report any skin lesions of morphology corresponding to erythema chronicum migrans. The skin biopsy was consistent with morphea diagnosis. The patient was treated with doxycycline, ceftriaxone and low doses of metyloprednisolone. Rapid, spectacular improvement of skin lesions was observed. Improvement of skin lesions after tretment with antibiotics led us to consider association between morphea and Borrelia burgdorferi infection.

The activity of mitochondrial respiratory system in intact peripheral blood mononuclear cells from multiple sclerosis patients

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Introduction. Neurodegeneration during the course of multiple sclerosis (MS) is associated with chronic inflammation and the production of reactive oxigen and nitrogen species, and mitochondrial injury.

Aim. The aim of this study was to evaluate the activity of mitochondrial respiratory system in peripheral blood mononuclear cells (PBMCs) from MS patients.

Material and Methods. The study included 15 multiple sclerosis patients hospitalized in Department of Neurology at Poznan University of Medical Sciences in Poznan, Poland and 23 healthy volunteers. PBMCs were isolated from EDTA blood via density gradient centrifugation (Histopaque, Sigma-Aldrich). The cell number was counted in Bürker's chamber and in YUMIZEN H500 (HORIBA, Japan) analyzer and the volume corresponding to $1x10^6$ cells was applied for respirometry. The activity of mitochondrial respiratory system was analyzed in intact PBMCs using high-resolution respirometer (Oxygraph-2k; Oroboros Instruments, Innsbruck, Austria) according to the ROUTINE, LEAK, electron transfer system (ETS), and residual oxygen consumption (ROX) protocol.

Results. ROUTINE respiration in PBMCs from blood was lower in MS patients (12.66 ± 3.77 pmol $O_2/s*10^6$ cells, mean ± standard deviation, P = 0,0480) than in controls (15.76 ± 4.54 pmol $O2/s*10^6$ cells). No changes in LEAK respiration were found in MS patients (4.25 ± 2.06 pmol $O2/s*10^6$ cells, P = 0.1431) compared to healthy subjects (4.52 ± 1.77 pmol $O2/s*10^6$ cells). ETS respiration in PBMCs from MS patients (14.44;

10.46 — 22.94 pmol $O2/s*10^6$ cells, median; interquartile range) did not differed from controls (16.54; 11.38 — 20.68 pmol $O2/s*10^6$ cells). Downregulation of ROX respiration was observed in PBMCs from MS patients (2.90 ± 1.70 pmol $O2/s*10^6$ cells) compared to controls (4.76 ± 1.79 pmol $O2/s*10^6$ cells, P = 0.0004).

Conclusions. Basic mitochondrial respiration is down-regulated in PBMCs along with inhibition of extramitochondrial respiration in the course of multiple sclerosis.

Rheological picture of Waldenström's macroglobulinemia

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Waldenström macroglobulinemia (WM) is defined by the World Health Organization as lymphoplasmacytic lymphoma (LPL). Increased concentration of IgM is one of the factors that lead to increase of blood viscosity. Blood hyperviscosity in patients with Waldenström's macroglobulinemia is serious clinical problem. The aim of this work was to observe the rheological parameters in a group of Waldenström's macroglobulinemia patients in a two year period. During this time the blood samples from each patient were collected four times. The evaluation included such factors as whole blood viscosity, plasma viscosity, hematocrit value and the tendency to aggregation and deformation of erythrocytes. The latter features were quantified using the mathematical rheological model of Quemada. Compared to the hemorheological parameters obtained for healthy objects, elevated value of plasma viscosity and an increased tendency to aggregation were observed in the studied group. Other rheological parameters values did not differ significantly form the values in healthy objects. All patients were under constant medical control.

Heart sarcoidosis — difficult diagnostic process and therapeutic management

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Sarcoidosis is granulomatous systemic disease of unknown — probably immune-related etiology with noncaseting granulomas involving usually lungs and lymph nodes, however it may affect different tissues and organs including heart. The disease affects at least 10 of 100,000 persons each year (more often women) at the age of 25–45 years old and individuals over 50 years old, with the highest prevalence in Europe and North America. The most devastating pattern of the disease is concerned with myocardial involvement which, according to different sources, is estimated between 5 and 50% of affected patients. Although cardiac sarcoidosis has usually benign, asymptomatic course, it accounts for approximately 25% of the disease-related deaths. The main cardiac symptoms include: (a) conduction disturbances (2nd and 3rd degree heart block), (b) ventricular arrhythmias (sVT) which may result in sudden cardiac death and (c) progressive heart failure. Despite this potential life-threatening symptoms, both, the diagnosis and management of cardiac sarcoidosis arouse controversy and remain challenging. According to HRS Expert Consensus (2014) there are histological as well as clinical pathways to a diagnosis of cardiac sarcoidosis. The first one embraces endomyocardial biopsy, and the second one that applies to patient with established extra-cardiac involvement, is based on the cardiovascular imaging (echocardiography, PET, CMR). The management strategies include immunosuppressive therapy (most often corticosteroids), antiarrhythmic drugs and invasive therapy (ablation, pacemaker/ICD) when indicated.

The main points of collaboration:

- Collaboration in the diagnostic procedures, especially in laboratory tests.
- Collaboration in the development of the heart sarcoidosis registry.

› Collaboration in the exchanging practical/clinical experience during mutual visiting possibilities.

Unobvious dermatological side effects of radiotherapy — report of two cases and literature review.

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Radiotherapy is one of the most common methods of treatment for malignant neoplasms. Typical side effects of radiotherapy include acute and chronic cutaneous reactions of varying intensity. However, rare causes of radio-induced skin diseases have also been reported.

We report two cases, in which treatment with radiotherapy have induced a localized bullous pemphigoid (BP) and a generalized morphea.

A 81-year old woman 3 months prior to hospital admission has received 33 courses of radiation therapy for an infiltrating duct carcinoma. In a day of receiving the last dose of radiation she has developed multiple tense blisters on the right breast. Direct immunofluorescence for antibasement membrane autoantibodies showed linear deposits of C3+ at the dermoepidermal junction. Multi-parametric indirect immunofluorescence ELISA assay had confirmed a high IgG antibody titer to BP230. IgG anti-BP180 antibodies were negative. The patient has been diagnosed with localized paraneoplastic radiotherapy-induced bullous pemphigoid and treated with a daily dose of 200 mg of oral doxycycline and 24 mg of oral methylprednizolone with a substantial improvement.

A 55-year old woman treated for a duct carcinoma of the left breast have presented at two years after mastectomy followed with chemo-radiotherapy with skin lesions characteristic for generalized morphea. A local reccurence of breast cancer has been excluded. The patient received a topical treatment with clobetasole and oral treatment with methotrexate in a dose of 7.5 mg daily. Due to lack of satisfactory response an UVA1 therapy has been started with good results — decrease of density of preexisting plaques, lack of new lesions, a "lilac ring" hasn't been observed.

Up to date, 37 cases of radiation-induced bullous pemphigoid and 88 cases of radiation-induced morphea have been reported in the literature. The cases described indicate the necessity of profound evaluation of skin changes in patients receiving radiotherapy.