DOI: https://doi.org/10.5114/fn.2020.102442

Abstracts from the Conference of Polish Association of Neuropathologists

CLINICAL AND EXPERIMENTAL NEUROPATHOLOGY

27 November 2020 (Webinar)

Neuronal tumours of the cervico-thoracic segment of the spinal cord

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We present two rare cases of neuronal tumors in the spinal cord including extraventricular neurocytoma and gangliocytoma.

The first patient was a 43-year-old woman admitted due to progressive weakening of the upper limbs, the lower-left limb and pain in the cervical spine. MRI with contrast showed an intramedullary solid-cystic tumour of the level C2-T5 (26 × 16.5 × 24 mm). The tumour was removed by C7-T1 laminectomy using multimodal intraoperative monitoring. Histopathological examination revealed groups of small uniform round cells forming Homer-Wright rosettes, cells with neuronal differentiation and mature ganglion cells (IHC: Synaptophysin+, Neurofilaments+, NeuN+, GFAP(–), Ki67– 1%, Olig2(–)). The lesion was diagnosed as extraventricular neurocytoma (I WHO).

The second case was a 13-year-old girl with a C6-T4 intramedullary tumor. The lesion was diagnosed during preoperative imaging due to scoliosis. Neurological examination was negative, MRI revealed an intramedullary mass of the C6-T4 level (26 × 19 × 48 mm). The tumour was removed by C6-T4 laminotomy using multimodal intraoperative monitoring. Histopathologically, it was composed of a irregular groups of mature ganglion cells focally with dysplastic geatures and a neuropil stroma and preexisting glial elements (IHC: Synaptophysin+, Neurofilaments+, NeuN+, GFAP+ in stroma, Ki67– 0, Olig2(–)). Gangliocytoma (I WHO) was diagnosed.

Both tumours are very rare in intramedullary location. The radiological characteristics of tumours is not pathognomonic. Complete removal of the lesion is a prerequisite for lasting and successful treatment effects. The carefull morphological assessment with immunophenotyping including glial and neuronal markers is necessary for the diagnosis.

Modeling *in vitro* of neurological disorders

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Modeling *in vitro* of early human neural development and neurological disorders is a challenge owing the lack of available animal models and ethical considerations. Due to species differences, it is impossible to extrapolate to humans data obtained for neurodevelopmental studies in rodents. On the other hand human embryonic stem cell (hESC) lines, which may closely reassemble *in vitro* early human development including neurodevelopment, are ethically controversial and not allowed in Poland.

Advances in stem cells technology allowing derivation of patient-specific human induced pluripotent stem cells (hiPSC) through the reprogramming of somatic cells enabled to set up hiPSC-derived *in vitro* human neurodevelopment and neuro-disease models, avoiding the destruction of human embryos. In addition recently developed hiPSC-derived three-dimensional emerging systems of cerebral organoids closely recapitulate not only human brain cell types and its architecture, but also their function. Functional modeling with cerebral organoids of normal versus pathological brain can be further extended by possibility to apply gene editing technology and new high-throughput culture strategies based on bioengineered microfluidic "organ on the chip" devices. All above provide emerging tools to model *in vitro* neurological disorders with the possibility of personalized as well as high-throughput studies in the field of basic research in disease models, drug discovery, toxicology and finally therapeutic applications including regenerative medicine.

This report presents state-of-the-art of the new strategies and applications of *in vitro* modeling of neurological disorders, highlighting technological advancement in the field.

Case of anaplastic ganglioglioma of cerebellum

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Seven years old boy was admitted with polycystic cerebellar tumour with calcifications revealed in CT study

performed after accidental head trauma. MRI examination showed lesion occupying whole vermis with only slight mass effect, infiltrating both hemispheres without clear borders. Contrast medium enhanced partially signal from the mass of tumour and also showed dispersed infiltration foci in whole cerebellum. Subtotal resection was performed. Mild postoperative cerebellar ataxia improved with rehabilitation.

Histological specimens showed heterogenous picture of glioneuronal tumour. Scant neuronal element differed from atrophying infiltrated cerebellar cortex, and included binuclear and enlarged cells. Large fields of the specimens contained glial component with features of pilocytic astroctrocytoma, with eosinophilic granular bodies, Rosenthal fibres, calcifications and microvessels proliferation accompanied by lymphoid infiltration. Tumour represented typical immunophenotype. Areas of higher cellularity with marked pleomorphism were also seen with pathologic mitotic figures. This finding, with Ki67 index elevated focally up to 20%, lead to diagnosis of anaplastic ganglioglioma, WHO GIII.

Further clinical observation supported by genetic profiling will be necessary for making decision on supplemental oncological treatment as the complete surgical resection is not possible.

Acute systemic inflammatory response alters expression of genes related to calcium homeostasis, epigenetic regulation, and lipid metabolism in hippocampus; relevance to Alzheimer's disease

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Aim of the study: Acute systemic inflammatory response (SIR) induces in the brain changes in the expression of genes involved in calcium homeostasis, oxidative stress, epigenetic regulation, lipid signalling, and cellular death. These changes may also contribute to the development of Alzheimer's disease (AD) neuropathology. Our aim was to evaluate gene expression pattern in the mouse hippocampus (MH) during SIR and compare them to human post-mortem hippocampal AD.

Material and methods: Gene expression in MH was analysed by using microarray technology 12 and 96 h after SIR evoked by intraperitoneal lipopolysaccharide (LPS) in adult C57BL6 male mice. The microarray data from human AD CA1-hippocampus was compared to age-, gender- and post-mortem interval-matched controls.

Results: It was found that 12 h after administration of LPS the expression of 231 genes in MH was significantly altered; however, after 96 h only the S100a8 gene encoding calgranulin A was activated. Gene ontology enrichment analysis demonstrated the alteration of gene expression related mostly to the immune-response. Significant increase of transcription of genes encoding lipid metabolism-related proteins was also observed. Moreover, the expression of genes coding proteins crucial for epigenetic regulation was altered: histone deacetylases and bromo- and extraterminal domain proteins. Remarkably, the significant alteration in expression of the same genes was found in the hippocampus of AD patients.

Conclusions: Our results suggest that SIR-induced changes of gene expression pattern may be crucial in AD pathogenesis/pathomechanism.

Support: Supported by the NCN (2018/31/B/NZ4/01379) (GAC) and an unrestricted grant to the LSU Eye Center from Research to Prevent Blindness (RPB); the Louisiana Biotechnology Research Network (LBRN) and NIH grants NEI EY006311, NIA AG18031 and NIA AG038834 (WJL).

Dual pathology (FCD and ganglioglioma) – the question of recognition

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Focal cortical dysplasia (FCD) and ganglioglioma (GG) are among the most prevalent causes of drug-resistant epilepsy in paediatric patients. Moreover, in some cases they coexist simultaneously co-creating potentially epileptogenic so called "dual pathology".

A histopathological examination of the surgical specimen from the frontal lobe tumor of the brain of a 14-year-

old patient with a 10-months history of seizures has been performed.

During the final examination of the specimen using HE and immunohistochemical staining (GFAP, Olig-2, ATRX, IDH-1, BRAF, p53, vimentin, synaptophysin, NeuN, CD34, Ki-67, EMA), typical FCD type 2b changes, including focal thinning/atrophy of the cortex, "balloon cells" and dysmorphic neurons, have been found. Apart from features of FCD there were also CD34-positive and BRAF V600E positive neuron-like cells within the astroglial background. Those are histopathological changes that could be hardly ascribed to FCD but suggested ganglioglioma.

As a result, although the prevailing histological picture corresponded to FCD type 2b, the presence of CD34-positivity in some cells as well as the BRAF V600E mutation though not forming a separate mass, but rather mixed component of the whole lesion speaks in favour "dual pathology" (here: the coexistence of WHO I/II ganglioglioma and FCD).

A reliable diagnosis of the coexistence of both pathologies regarding the lack of clear and unequivocal morphological features of typical and separate ganglioglioma is neither easy nor straightforward. All this is a question of recognition...

Neural component of the solid tumors microenvironment

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Relations between cancer and the nervous system are considered as a new hallmark of cancer. There are preclinical and clinical evidences that the central and peripheral nervous system contributes to tumor initiation and progression. Sympathetic and parasympathetic nervous system control different aspects of cancer growth. The origin of nerves in cancer stroma remains unknown. Nerves within tumor microenvironment control cellular interactions, angiogenesis, immune system by releasing neurotransmitters and neuropeptides. Axon guidance molecules and neurotrophic factors regulates axonogenesis and neurogenesis in cancer which are phenomenons responsible for tumor innervation. Relations between the nervous system and cancer may be characterized as a perineural invasion (PNI) or nerve density (ND) as marker of axonogenesis, which may be studied immunohistochemically, radiologically, genetically, or in outgrowth assays. PNI is one of the ways of spreading cancer and creates a perineural niche, which additionally supports tumor growth. The neural component of the tumor stroma is an important part of the complex neoplasm phenotype, which may be potentially a new prognostic factor and therapeutic target. We described prostate cancer as a model tumor for neural relations and regulation research. We showed that ND in prostate cancer is altered. Neuropeptide Y is a neurotransmitter which links autocrine and paracrine regulation of prostate cancer biology. Neurobiology of cancer has emerged as a new fascinating area of research. Results of preclinical and clinical studies showed, that relations between cancer and microenvironment may be new options for broadening the therapeutic landscape in oncology, because the activity of nerves may be modified genetically, surgically, or pharmacologically.

Role of advanced magnetic resonance imaging techniques in multiple sclerosis

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that is characterized by inflammation, demyelination and degenerative changes. The clinical use of Magnetic Resonance Imaging (MRI) in patients with MS has advanced markedly over the past few years. The benefits of the 2010 McDonald MRI criteria included the focus on lesion location; the presence of gadolinium-enhancing and gadolinium-non enhancing lesions allows very early diagnosis in some patients who undergo a single MRI examination at any time after symptom onset. During the last decades, the effort of establishing satisfactory biomarkers for multiple sclerosis has been proven to be very difficult, due to the clinical and pathophysiological complexities of the disease. MRI has been new biomarker and crucial in the development of anti-inflammatory disease-modifying treatments. The current landscape of multiple sclerosis clinical trials is currently expanding to include testing not only of anti-inflammatory agents, but also neuroprotective, remyelinating, neuromodulating, and restorative therapies. This is especially true of therapies targeting progressive forms of the disease where neurodegeneration is a prominent feature. Imaging techniques of the brain and spinal cord have rapidly evolved in the last decade to permit *in vivo* characterization of tissue microstructural changes, connectivity, metabolic changes,

neuronal loss, glial activity, and demyelination. Advanced magnetic resonance imaging techniques hold significant promise for accelerating the development of different treatment modalities targeting a variety of pathways in MS.

Onconeurology

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Onconeurology is a term proposed as the opposite of neurooncology. It emphasizes the need for care in patients who manifest neurological deficits as systemic malignancy complications (e.g., neurological paraneoplastic syndromes) or its treatment (chemo- and/or radiotherapy).

Exposition to radiation induces direct toxicity, particularly in white matter/myelin producing cells (both oligodendrocytes and Schwann cells) and in endothelium leading to "islet" endothelial proliferation, vessel occlusion, ischemia, and necrosis. Moreover, due to strong microglial inflammatory response and production of pro-inflammatory cytokines (interleukin 6 and tumor necrosis factor α), neuronal precursor cells, which participate in neurogenesis in the hippocampus, are separated from the vascular niche. As a result, several neuropathological changes are radiotherapy complications: myelin and axonal loss, spongiosis, white matter gliosis, thickening of small vessels in deep areas of white matter caused by vascular fibrosis, and atherosclerotic changes in large arteries of Willis circle.

Acute encephalopathy is observed in up to 50% of patients during radiation and manifests as headaches, somnolence, and focal neurological deficits. MRI examination can be normal, and the prognosis can be fair.

Early complications manifest within 1-3 months after radiotherapy as somnolence, nausea, anorexia, or transient cognitive impairment and are related to demyelination that MRI reveals as hyperintensity in T2 weighted images. Tumor pseudoprogression develops as an early complication in up to 30% of glioblastoma multiforme patients treated with temozolomide and radiotherapy. It manifests as a focal neurological deficit. Tumor necrosis, vascular lesion, and inflammation are involved pathomechanisms, and MRI reveals contrast enhancement.

Late complications include necrosis, mild cognitive impairment, or leukoencephalopathy with cognitive functions deterioration, which develops within months to years after radiotherapy. Pathogenesis of late complications is associated with vascular lesions, necrosis, and cellular changes, and MRI shows hyperintensities in T2 weighted images, cysts, and contrast enhancement. MR spectroscopy reveals an increase in choline or free lipids peaks.

At the level of the spinal cord, radiotherapy causes myelopathy with acute or delayed onset. Neuropathological changes related to radiation include demyelination, spongiosis, vascular hyalinosis, perivascular fibrosis, and myelomalacia.

Plexopathy belongs to radiotherapy's neurological complications in the peripheral nervous system and requires differential diagnosis with tumor infiltration.

To conclude, onconeurology seems to be clinicopathological that requires attention because of the growing number of oncological patients who manifest neurological complications due to improved treatment effectiveness and prolonged survival.

Investigation of alterations in small nerve fibers and local neurogenic mechanisms in vulvar lichen sclerosus

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Introduction: Lichen sclerosus (LS) is a chronic inflammatory disease affecting mainly anogenital skin. Skin lesions are accompanied by severe pruritus, pain and burning sensation. Persistent and frequently poorly responding to topical treatment sensory symptoms seriously impact patients' quality of life.

Aim of the study: To investigate whether in vulvar LS tissues occur changes in innervation (PGP 9.5, CGRP, GAP-43) and differences in expression pruritic receptors (opioid receptor μ, PAR-2), and in number of mast cells in comparison to normal vulvar tissues.

Material and methods: Immunohistochemical stains were performed on 20 FFPE biopsies of vulvar LS and on 20 samples of normal vulvar skin. The adapted protocol conceptually based on evaluation of intraepidermal nerve fibre density (IENFD) in diagnosis of small fibre neuropathy was applied.

Results: There was significant decrease of IENFD, marked with PGP 9,5 (5.92/mm vs. 11.47/mm, $p = 0.0049$) and GAP-43 (7.2/mm vs. 17.68, $p = 0.013$) and increase of IENFD of CGRP-positive nerve fibres (6.26/mm vs. 3.38, $p = 0.03$) in vulvar LS tissues.

The significant increase of expression of opioid receptor μ in leukocytes ($p = 0.01$), PAR-2 receptor in endothelial

cells (p = 0.0002), and in mast cells around dermal nerves (p = 0.04) in vulvar LS skin was observed.

Number of mast cells located under epidermis, in dermis, and around dermal nerves was increased in LS group with statistical significance (respectively 17.5 vs. 8, p = 0.0005, 46 vs. 24.5, p = 0.01, 5 vs. 2, p = 0.002).

Conclusions:

1. The investigation showed alterations in skin innervation, expression of pruritic receptors and number of mast cells in vulvar LS.
2. The observed changes may possibly contribute to the pathomechanism of sensory symptoms in LS.
3. The increase of expression of opioid receptor μ and PAR-2 receptor and the increase in number of mast cells demonstrate the involvement of non-histaminergic mechanisms and neuroinflammation in development of vulvar LS.

The journal "Neuropatologia Polska" (1963-1993) – the beginnings and activity outline

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After the Second World War, the tedious process of rebuilding the community of Polish neuropathologists and their organizations began. The appearance of the scientific journal 'Neuropatologia Polska' in 1963 was the turning point. The first editorial office of this periodic included the later fames of Polish neuropathology: Adam Kunicki (Editor), Ewa Osetowska (Deputy Editor), Mirosław J. Mossakowski (Secretary), Henryk Wiśniewski (Technical Secretary). Between 1963 and 1964 the journal was published twice a year, later once a quarter. The articles were published mainly in Polish, but also in French and English. Main editors were: Ewa Osetowska, Mirosław J. Mossakowski, Irmina B. Zelman and Maria Dąmbska. Since 1991, the journal had been published in English. The last, XXXI volume of "Neuropatologia Polska" was published in 1993. In total 1,338 texts on 15,735 pages were published in the years 1963-1993. Currently, it is continued (with continuous numbering) as "Folia Neuropathologica" (Editor-in-chief, prof. Ewa Matyja). In 2019, a research group started a project aimed at evaluation of the journal achievements.

Free Neuropathology: a high-quality, diamond open-access neuropathology journal run entirely by neuropathologists – the first eleven months

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Based on the hypothesis that a diamond open access neuropathology journal of a high scientific and technical quality can be run entirely by neuropathologists, we launched Free Neuropathology (FNP; freeneuropathology.org) in January 2020. Classical publisher activities, such as copyediting, layout, website maintenance, long-term preservation of articles, and journal promotion, are undertaken by neuropathologists and neuroscientists along with scientific librarians using free open access software. The journal is free for both readers and authors, and papers are published under a Creative Commons BY SA licence, where copyright remains with the authors. Based on 33 articles published by November 2020, it takes FNP 11.7 days from submission to first decision. High-quality copyediting, layout, and online publishing in the final format is accomplished in a mean of 7.1 days. Absence of a commercial publisher enables democratic and scientifically-driven decisions on editorial structure, website design, journal promotion, paper formatting, special article series, and number of accepted papers. The editorial structure enables swift implementation of new categories of papers. Ongoing activities include steps towards bibliometric indexing, exploring novel types of publishing, and promoting free opinion by opinion piece articles and software enabling sentence-level comments about any published paper. This new model of journal publishing, which returns the control of scholarly communication to scientists, will be of interest to neuropathologists and the wider scientific community alike.

Antiproliferative effects of CK2 inhibitors on U-87 MG glioma cell line

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Aim of the study: High grade gliomas are the most common and invasive primary brain tumours leading to poor survival and prognosis. Caseine kinase II (CK2) is an ubiquitous Ser/Thr protein kinase present in both the nucleus and cytoplasm of cells. CK2 has been frequently found to be deregulated in variety of cancers. It plays a role in cell survival, proliferation and can exert an anti-apoptotic effect. CK2 inhibitors have been suggested as promising drugs for antitumour therapy. The aim of this study was to evaluate the cytostatic effect of new CK2 inhibitors on U-87 MG human primary glioblastoma cell line.

Material and methods: We examined the cytotoxic effect of selected CK2 inhibitors: 1) 2-aminoetyloamino-4,5,6,7-tetrabromo-1H-benzimidazol, 2) 4,5,6,7-tetrabromo-N-2-metylo-N-2-hydroksy-etylo-2 aminobenzimidazol; 3) 1-(β-D-2'-deoxy-ribofuranosyl)-4,5,6,7-tetrabromo-1H-benzimidazol, against glioma U87 MG cell line. The viability of neoplastic glioma cell lines was established at 24 hours post tested CK2 inhibitors treatment with by Cell Titer 96®AQueous One Solution Cell Proliferation Assay.

Results: In all experimental groups there was a marked decrease of the total number of U87 MG glioma cells after 24 hours of treatment. Neoplastic cells treated with CK2 inhibitors also showed a statistically significant decrease of viability in comparison to the control cultures. Amongst tested CK2 inhibitors, 2-aminoethylamino-4,5,6,7-tetrabromo-1H-benzimidazole appeared to be the most effective and exhibited the strongest anti-proliferative effect. Moreover, this compound elicited the strongest inhibitory effect on the viability of cultured U87 MG cells at a concentration of 100 μM after 24 hours.

Conclusions: The results show that CK2 inhibitors, most notably 2-aminoethylamino-4,5,6,7-tetrabromo-1H-benzimidazole, have a potent antiproliferative efficacy against U87 MG glioma cells. Therefore, the tested CK2 inhibitors may be considered as a potentially promising anti-tumour therapy, including the treatment of glioma-derived primary malignant brain tumours.

Acknowledgements: The research was supported by the grant 2019/03/X/NZ3/00954 National Science Centre, Poland and partly supported by the Foundation for the Development of Diagnostic and Therapy in Warsaw.

Neuropathological aspects of COVID-19

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Since December 2019 COVID-19 has caused death of 1,4 mln people worldwide, including 400,000 Europeans. Many reports and first studies indicate a significant role of the nervous system in the COVID-19 disease.

Poster presents SARS-CoV-2 clinical and neuropathological manifestations, including pathobiology and post-COVID syndrome. Neurotropic properties of SARS-CoV-2 are attributed to inter alia transport by synaptic connections from peripheral nerves to the central nervous system via cranial nerves or by the interaction of the virus and the ACE2 receptor in the nasal cavity and the mouth. Lack of virus replication does not guarantee neither complete remission of existing symptoms, nor the possibility of developing new COVID-19 symptoms, which is called post-COVID syndrome. This phenomenon is attributed to autoreactive T cells and antibodies. Post-mortem studies of SARS-CoV-2 positive patients indicate mainly mild inflammatory lesions of brainstem.

Diffuse microglia activation with individual microglia clumps was observed in 86% of patients, with the strongest expression in the brainstem and cerebellum. Positive HLA-DR staining in subarachnoid and subependymal areas was not typical of classic meningitis. Infiltration of the meninges by cytotoxic T cells with macrophages IBA-1 (+), CD68 (+) and TMEM119 (–) was described in 79% of patients. Increased expression of genes: ACE2, TMPRSS2, TPCN2, TMPRSS4, NRP1 and CTSL in the cerebral cortex may be responsible for susceptibility to SARS-CoV-2 invasion of the nervous system. It is found in glial cells, neurons, and endothelium. Slight cytotoxic T cells infiltration was observed mainly in the frontal cortex, basal ganglia, and perivascular regions of the brainstem. In the olfactory bulb cytotoxic T cells infiltration was minor, while high-grade astrogliosis and microgliosis were described. Neuropathological changes did not correlate with the severity of clinical symptoms. It is necessary to conduct further research.

Modeling of MMP/TIMP system in biomarkers spectrum of neurological and neuromuscular disorders

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The system of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) is being deeply studied under physiological/pathological conditions (Cardiovasc Res 2006; 69(3): 562-573; Biomolecules 2020; 10(5): 717; Cells 2020; 9(5): 1313). The mechanism/relationships of the MMP/TIMP system are not yet known. Many researchers have shown that MMPs and TIMPs levels change in neurological (Alzheimer's, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis (ALS) or stroke patients) and neuromuscular disorders. Furthermore, it should be noted that heart disease is a common clinical manifestation of neuromuscular disorders, particularly muscular dystrophies (MDs). MDs are a heterogeneous group of inherited diseases with different molecular/genetic bases, but similar clinical features and dystrophic changes. In the case of heart muscle, dystrophic processes can affect myocardial cells as well as specialized conducting fibers (Physiol Rev 2007; 87(4): 1285-1342; Int Heart J 2019; 60(1): 12-18). Cardiac features seen in patients with Duchenne/Becker muscular dystrophy, myotonic dystrophy or Emery-Dreifuss muscular dystrophy (EDMD).

The purpose of the research was to estimate the importance and relationship of MT1-MMP, MMP-2,-9 and TIMP-1,-2,-3 (their levels were determined by ELISA) in patients with: (a) mild/severe progression of ALS, and (b) different AD- or X-EDMD forms, using the applied statistical intelligent models of classification and pattern recognition (IEEE Trans Pattern Anal Mach Intell 2000; 22(1): 1-37; JILSA 2017; 9: 1-16; Biomech Model Mechanobiol 2020, online: 16 July). ALS is a progressive neurodegenerative disease characterized by the loss of motor neurons in the spinal cord, brainstem, and motor cortex that dramatically reduces life expectancy (Folia Neuropathol 2011; 49(1): 1-13; Front Neurosci 2019; 13: 1310). EDMD, a rare inherited disease, is clinically characterized by humero-peroneal muscle atrophy and weakness, multijoint contractures, spine rigidity and heart failure (Folia Neuropathol 2016; 54(1): 1-8; Muscle Nerve 2020; 61(4): 436-448). The results of the proposed analytical modeling of the MMP/TIMP system indicated a vector of features/biomarkers: (a) MMP-2 CSF (and EPO) may be the best one for differentiating ALS progression, and (b) the set of serum biomarkers {MT1-MMP,MMP-2,TIMP-1} allows clinicians to recognize the state of patients with AD- vs. X-EDMD.

In conclusion, the experimental/clinical and modeling studies on the MMP/TIMP system indicate that the system may play an important role in therapeutic (early cardiac intervention, monitoring) applications and diagnostic/prognostic values in future ALS and EDMD disorders.

Applications and perspectives of virtual posturography in neurological and neuromuscular disorders

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The vertical stable position of the human body is possible by the work of a complex posture control system, which also requires proper operation and cooperation of many (systems) senses. Postural control is "difficult" for the older adults, and it can also be impaired by various disorders. There are many methods of assessing the postural stability, among which modern innovative information technologies (IT) and artificial intelligence play an important role (Folia Neuropathol 2019; 57(4): 391-393; Front Neurol 2020; 11: 7). An example in clinical practice is virtual posturography used in physiotherapy, in supporting the development of children with disabilities, in pro-health (falls) prevention, including degenerative neurological and neuromuscular disorders (Alzheimer's, Parkinson's, ALS, multiple sclerosis diseases or muscular dystrophies), and elderly, also in neuropsychological or post-traumatic rehabilitation (Clin Interv Aging 2019; 14: 1567-1577; J Clin Transl Res 2020; 5(4): 148-154).

In the presented research on the assessment of postural balance, the virtual NEUROFORMA system (https://neuroforma.pl/) was used also equipped with a (virtual) posturographic platform. The system offers a wide variety of interactive and engaging cognitive, movement and balance exercises. They are implemented in the form of serious games (in virtual sessions), under the visual control of the exercising subject, and in accordance with the promotion/evaluation algorithm depending on the scores achieved. The test results confirm the usefulness and sensitivity of virtual posturographic methods in the assessment of balance both in health conditions (for balance training and eye-hand coordination, here additionally in training forms with biofeedback and balancing options),

and in disease states (interactive therapeutic and improving activities, neurorehabilitation).

In summary, virtual posturography is an IT with high potential and prospects for application in many fields of the 21st century medicine, especially in the modern practice of neurological/ cognitive-motor rehabilitation, and in geriatrics. It is based on methods of static/dynamic posturography. These technologies are not only attractive in form, but also sensitive to changes in both physical activity and emotional or cognitive behavior (attention, memory, language, visual-spatial functions). An additional advantage of the innovative VR technologies is the fact that both specialized versions for medical centers and personalized systems for use by subjects at home are created.

Digital Brain – digital collection of the Institute Psychiatry and Neurology

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The aim of "Digital Brain" project is to create the digital archive of that unique collection of the Department of Neuropathology of the Institute of Psychiatry and Neurology in Warsaw collected for over half a century. The collection comprises a set of brain fragments fixed in buffered formalin solution, paraffin blocks, histological and immunohistochemical specimens and neuropathological protocols.

Our collection include over five thousands of brain's fragments, neurological disease, mental illnesse, tumors, and childhood diseases, as well as brains from donors with very rare protein mutations, for example Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jacob disease, Huntington's disease, Wilson's disease, Down syndrome.

Using the state-of-the-art technological and IT solutions, we have created a tool for scientists and medical professionals community. The www.digitalbrain.ipin.edu.pl database will be available free of charge, in open formats and without registration. That form of knowledge popularization will give both specialists and interested members of the general public easy access to scientific and teaching materials.

The project "Digital Brain" is co-funded by the European Union and the Polish budget (Project No. POPC.02.03.01-00.0042/18-00).

Neuromorphological examination of early-onset Alzheimer's disease

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Introduction: Alzheimer's disease is the most common cause of dementia at older age globally today and it is a progressive neurodegenerative disease most often associated with cognitive decline and memory deficits. Statistical data reveals that over 30 million people are suffering from Alzheimer's disease worldwide and this number is estimated to double every 20 years to reach 66 million in 2030 and about 115 million by 2050. Early-onset of the disease can begin when people are in their 30s or 40s and it is important to diagnose the disease at an early stage at a young age.

Aim of the study: To investigate the neuromorphological features of brain damage among early-onset patients with Alzheimer's disease.

Material and methods: The medical history of 25 patients with early-onset Alzheimer's disease were studied and morphological examination of brain was performed. Consent for postmortem examination was asked from patients. The study was conducted in accordance with research regulations and conformed to the Declaration of Helsinki.

Results: Neurological examination showed prominent apraxia and mild memory dysfunction. Only half of patients with early-onset Alzheimer's disease had memory impairment. The mean age of first symptoms was 48 ±3 years for the patients. Clinical manifestations of our patients with early-onset Alzheimer's disease included apraxia and visuospatial dysfunction and an aphasic-apraxicagnosic syndrome. MRI of the brain showed mild and moderate parietal atrophy in half of cases without medial temporal and frontal lobe atrophy. Some patients had neurological problems with language dysfunction, they had problems with a fluent speech, understanding of sentences, comprehension of single words and difficulties in picture naming. MRI of the brain was mostly found pathology in the frontotemporal lobes. The pathologic diagnosis

of Alzheimer's disease is the gold standard for diagnosis. Some topographic features of Alzheimer's disease can be ascertained on macroscopic examination, no single feature or combination of features is specific. A neuropathologic diagnosis of Alzheimer's disease showed amyloid plaques, neuritic plaques, neurofibrillary tangles composed of filamentous tau proteins and cerebral amyloid angiopathy.

Conclusions: Clinical and pathological studies of early onset Alzheimer's disease are necessary to further search for diagnostic criteria and to establish correlation between clinical symptoms and damage of brain areas for differential diagnosis with other neurodystrophic processes.

Subcortical leukoencephalopathy or Binswanger's disease: morphologic basis of cognitive impairment and dementia

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Introduction: Binswanger disease is a progressive neurological disorder caused by arteriosclerosis and thromboembolism blood vessels of white-matter and basal ganglia or thalamus in the setting of dementia. The white matter lesions are the main pathologic characteristic of Binswanger's disease. Patients with Binswanger disease have a history of strokes or transient ischemic attacks and signs of this disease develop in a stepwise fashion in contrast to gradually progressive course of Alzheimer disease.

Aim of the study: To investigate the neuropathological substrates of cognitive impairment and dementia in Binswanger disease in order to ensure the reliability of the diagnosis.

Material and methods: Seven patients with a clinical diagnosis of microangiopathic encephalopathy of Binswanger and cognition impairment were studied. The microscopic study of brain tissue was done.

Results: Clinical manifestations of our cases included emotional incontinence, frontal executive dysfunction of brain, gait problems, urinary incontinence and dementia. MRI identified areas of periventricular hyperintensity on T2-weighted images. White matter pathology accompanied ventricular enlargement and lacunar infarcts in the basal ganglia and thalamus. Gross pathology showed variable involvement of the white matter, which may be superficial and subcortical or extend deep into the white matter to periventricular sites. The structural basis of disadaptation and attenuation of intellectual mnestic functions in Binswanger encephalopathy are two types of capillaropathy, mainly subcortical structures: obstruction of the lumen of the vessel and capillary stagnation as a result of chronic "retrograde venous support", due to which the blood filling of the vessels remains at a relatively high level. Both types are accompanied by diffuse ischemia of the white subcortical substance (subcortical leukoencephalopathy) due to the permeability of the capillary wall. Vascular dysfunction of microhemocirculatory bed leads to the development of many pericapillary microinfarctions. Vessels show marked arteriolosclerosis with hyalinization. The genesis of dementia in Binswanger's encephalopathy is associated with "disconnection-syndrom", with the separation of cortical subcortical connections as a result subcortical white matter damage, and with dysfunction of the basal ganglia and thalamus.

Conclusions: Binswanger's encephalopathy is characterised by arteriolosclerosis, lacunar infarcts and cortical and subcortical microinfarcts and diffuse white matter changes, which involve myelin loss and axonal abnormalities and neuropsychological evidence of executive dysfunction.

Rasmussen encephalitis: a clinicopathologic study of rare disease

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Introduction: Rasmussen encephalitis is a rare and severe immuno-mediated brain disorder that is associated with unilateral hemispheric atrophy and affects mostly children or young adults and manifests as severe refractory epilepsy, hemiplegia, defects of motor and speech functions, and cognitive impairment.

Aim of the study: To investigate the clinicopathologic features of Rasmussen encephalitis and to increase understanding of this rare disease.

Material and methods: The disease history of a twenty-eight-year old boy with a twenty-year history of Rasmussen's encephalitis and a clinical-morphological comparison with data of autopsy studying is described.

Results: The clinical manifestations included epilepsia partialis continua and progressive neurologic deficits in 28-year-old young man, suffered from Rasmussen's encephalitis over 20 years. Disabled childhood group I, repeatedly treated inpatient. EEG recorded slow activity above the surface of the affected area. Neuroimaging MRI

revealed progressive unilateral focal cortical atrophy of the frontal lobe, gray and white matter high-signal changes with basal ganglion involvement. According to relatives, the frequency and severity of epileptic seizures have increased over the past 3-4 years. Antiepileptic therapy was not effective, death was ascertained. At the autopsy the hemispheres were asymmetrical. Frontal and partially parietal lobes of the left hemisphere moderately reduced in size, cerebral cortex thinned to 3-4 mm, gray-pink, white matter slightly compacted with small 1-2 mm hemorrhages, the lateral ventricle pronounced dilated and contains transparent cerebrospinal fluid, the left subcortical nuclei – caudate and lenticular expressed thinned. Left temporal and occipital lobes were the usual sizes. Histopathological features of perivascular lymphocytic infiltrate, microglial activation with microglial nodules, and reactive astrocytosis with or without evidence of neuronophagia, dystrophic changes of neurons with homogenization of the cell cytoplasm, karyopyknosis, shadow cells confirmed a diagnosis of Rasmussen's encephalitis. Spongy edema and cavitation were seen in focal cortex. Another histopathologic features in our case was an ectopic neuron in subcortical white matter in one of the slides of an atrophic frontal gyrus.

Conclusions: Rasmussen encephalitis is a rare and immune-mediated brain disease with progressive unilateral hemispheric atrophy and it is important to recognise this disease as early as possible. It is proposed that an accurate clinical evaluation and histopathological grading of these lesions may possibly have a role in patient prognostication.

The use of neurosurgical 3D exoscope in the surgery of tumours in the pineal region

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Introduction: Supracerebellar infratentorial approach to the pineal region is technically challenging and requires adequate visualization. VITOM®-3D exoscope is the double lens camera mounted on flexible arm. This device is smaller than microscope and allows more comfortable position of surgeon during the procedure without any visual compromise.

Aim of the study: We report series of patients with a tumor in pineal region treated with the assist of the neurosurgical exoscope.

Material and methods: We prospectively enrolled 4 patients with tumor in pineal region. The surgery with the assist of VITOM®-3D exoscope was performer. Every patient was radiologically assessed pre- and postoperatively.

Results and discussion: 4 patients were successfully operated. The average length of hospital stay was 10,75 days. One patient presented with postoperative nystagmus that postoperatively resolved. In postoperative MRI complete resection was noted in every case. No complications were noted.

Position of surgeon during the procedure was more comfortable without excessive extension of arms. Visualization and lighting was optimal without the need to constantly correct the focus and position of the exoscope.

Conclusions: Due to better comfort and vision for the surgeon, better quality of tissue sample was obtained what allows pathologist to effortlessly describe the material.

The influence of a sphingosine-1-phosphate receptor modulator, fingolimod, on the expression of genes encoding selected presynaptic proteins in a brain cortex of Alzheimer's disease mice

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One of the symptoms of neurodegeneration in Alzheimer's disease (AD) is dysfunction of synaptic transmission, which is regulated by specialized presynaptic proteins. On the other hand, decreased levels of sphingosine-1-phosphate (S1P), a bioactive sphingolipid that exerts a prosurvival effect through specific receptors, were observed in the brains of AD patients. Treatment with fingolimod, a S1P receptor modulator, had a positive impact on the disease progression in animal models of AD; however, its effect on presynaptic proteins in AD is unknown. Therefore, the aim of this study was to investigate changes in gene expression of selected presynaptic proteins in

a brain cortex of AD mice and to determine the influence of fingolimod on these processes.

The experiments were conducted on the brain cortex of 3- and 12-month-old FVB mice: with overexpression of the human mutant gene of β-amyloid precursor protein (FVB-APP+) and without the transgene (FVB-APP–), which received fingolimod (1 mg/kg bw, i.p.) or its vehicle (0.9% NaCl) for 2 weeks. The expression of genes encoding the following presynaptic proteins: synaptobrevin-1 (VAMP1), syntaxin-1a (STX1a), synaptosomal-associated protein 25 kDa (SNAP-25), complexin-1 (CPLX1), synaptotagmin-1 (SYT1), synaptophysin-1 (SYP1) and neurexin-1 (NRXN1) was investigated using the qRT-PCR method. The statistical analysis of the results was performed using the two-way analysis of variance with Tukey's post hoc test.

A significant reduction in expression of Vamp1 was found in a brain cortex of 3-month-old FVB-APP+ mice. Administration of fingolimod had no influence on any gene expression in this age group. In 12-month-old transgenic animals, a significant decrease in Vamp1 and Nrxn1 expression was observed. In contrast to younger mice, the administration of fingolimod to 12-month-old FVB-APP+ animals increased the expression of Vamp1, Syt1, Stx1, Cplx1 and Snap25.

Changes in the expression of the studied genes in a brain cortex were observed in both age groups with similar frequency. It is noteworthy that the expression of Vamp1 was significantly decreased regardless of an animal age. Administration of fingolimod to 12-month-old transgenic mice increased the expression of most analysed genes to control values (FVB-APP–).

Supported by grant no. NCN 2014/15/B/NZ3/01049 and statutory budget of MMRC, theme no. 7.

Pathology of neurodegenerative diseases

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Neurodegenerative diseases (ND) affect millions of people worldwide. These diseases are associated with multiple risk factors, but the risk of being affected by a neurodegenerative disease increases dramatically with age. Such diseases are incurable, resulting in progressive degeneration of structures and death of neurons. Neurodegenerative diseases are associated with the accumulation of intra/extra cellular pathologenic proteins. These proteins are either incorrectly produced/configured or incorrectly cleared from organs by secretory systems such as the hematopoietic, lymphatic and glymphatic systems. The most frequently aggregated proteins in these disorders are the following proteins: amyloid β-protein, Tau-protein, α-synuclein, and TDP-43, transthyretin and prions. In ND, deposits of pathologenic proteins are found in the cells of the central (CNS) and peripheral nervous system (PNS). Peripheral nervous system – the part of the nervous system that transmits information between the central nervous system and individual organs. The peripheral nervous system also includes the enteric nervous system, which contains five times more neurons than the CNS. Pathological protein deposits are observed primarily in nerve cells but also in other cells of organs and blood vessels. In the central nervous system these proteins to form disease-characteristic aggregates, such as amyloid plaques and neurofibrillary tangles in Alzheimer's disease or Lewy bodies in frontotemporal lobar degeneration/Parkinson's disease or Pick bodies in Pick disease. In the cells of the peripheral nervous system, protein deposits do not form characteristic morphological forms, as α-synuclein deposits in the ganglia of the interic nervous system. In the course of ND we observe clinical symptoms resulting from damage to many systems and organs. Neuropathological changes as well as pathological changes of the peripheral nervous system indicate that ND diseases are systemic diseases. Identifying all pathogenic proteins accumulated in ND, identifying neuroanatomical structures and describing the dysfunctions of systems responsible for removing abnormal substances from the body, will accelerate the development of biomarkers of ND diseases.

Surgical treatment of tumors of the cerebellopontine angle using exoscopic imaging and an ultrasound knife – presentation of the method and preliminary results

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Introduction: The aim of this study is to present the preliminary results of surgical treatment of cerebellopontine angle tumors with the use of a new, exoscopic imaging method and the use of an ultrasound knife.

Material and methods: Tumour resection of the cerebellopontine angle with the use of an exoscope and an ultrasound knife was performed on 3 patients: a 30-year-old woman, a 59-year-old woman and a 63-year-old man.

The operations were performed in a sitting position, with the operator behind the patient. The craniotomy was performed using an ultrasonic knife (instead of the traditional method of drilling a trepanation hole and using a craniotome). Instead of a microscope, a VITOM® exoscopic camera (Karl Storz GmbH & Co., Tuttlingen, Germany) was used for imaging.

Results: A complete resection of the pathological mass was performed in all treated patients. In the histopathological examination, Schwannoma was diagnosed in each of the three cases (I WHO).

After the surgery, no new neurological deficits were observed in any of the patients. The use of an ultrasonic knife was not related in any of the cases with damage to the dura mater.

A bone flap was restored in each of the patients. Postoperative fluids leakages were not observed in any of the patients. Hospitalization time for all patients was 8 days.

Conclusions: Based on the preliminary results, it can be assumed that the presented technique with the use of modern technologies such as an exoscope and an ultrasound knife is a potentially safe and effective form of treating tumours of the cerebellopontine angle. Modification of the classic technique with the use of a microscope did not involve additional complications or longer hospitalization time. However, further studies involving a larger population of patients are necessary.