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Ulrastructural changes of skeletal muscle in spinal and bulbar muscular atrophy (SBMA)

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Introduction: Spinal and bulbar muscular atrophy (SBMA, Kennedy's disease) is an X-linked recessive disease affecting lower motor neurons. According to current knowledge, changes in skeletal muscles are secondary to depletion of motor neurons. However, growing body of evidence suggest that muscle changes can be also a primary process.

Method: Muscle biopsy was obtained from a 62-year old patient with genetically confirmed SBMA. Properly prepared ultrathin muscle sections were examined with an Opton DPS 109 transmission electron microscope.

Results: Electron microscopy revealed neurogenic abnormalities: large-diameter (hypertrophic) fibres with identifiable sarcomeres and prominent disruption and loss of myofilaments; small-diameter fibres with mostly disorganized sarcomere structure with only focal clusters of myofilaments, Z line abnormalities such as their duplication and rod-like structures and cytoplasmic bodies, composed of a dense core surrounded by a halo with radiating filaments. Numerous nuclei often with irregular shapes had different condensation and distribution of chromatin from dispersed to highly condensed, like pyknotic nuclei. Occasionally electron-dense inclusions in nuclei were found. There were also visible some myogenic features: hypertrophic, angular fibres with few nuclei with normally condensed chromatin and proliferation of connective tissue between damaged muscle fibres.

Conlcusions: Ultrastructural changes of SBMA skeletal muscle are characterized by amount of neurogenic atrophy, together with small changes suggestive of muscle disease. It is possible that myogenic alternations are additional primary process associated with accumulation of affected receptor proteins in skeletal muscles.

Intracerebral hemorrhage in patient with cerebral amyloid angiopathy treated with thrombolysis due to ischemic stroke

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Cerebral amyloid angiopathy (CAA) is one of the important cause for intracerebral hemorrhage (ICH). It is often under diagnosed due to lack of routine immunohistological examination of the blood vessels.

A case report of 78 year old male admitted to the Second Department of Neurology in the Institute of Psychiatry and Neurology due to acute stroke is presented. CT brain scan done during first 3 hours from the onset of symptoms revealed only hyperdensity in the right middle cerebral artery. The ischemic stroke was diagnosed. The patient was treated with recombinant tissue plasminogen activator (rtPA). In anamnesis he had coronary heart diseases, heart infarct with coronary artery bypass graft (CABG), diabetes type 2 and hyperlipidemia. In neurological examination he was sleepiness with eye skew deviation, left hemianopsia, left hemiplegia and left Babiński sign. CT brain scan done after 24 hours revealed a big ischemic stroke with secondary intracerebral hemorrhage localized in the right frontal lobe and basal ganglia with brain edema. The National Institutes of Health Stroke Scale (NIHSS scale) was 20 points. Patient died in the third day of hospitalization. The autopsy was performed. The sliced brain speciments were stained immunohistologically with antibodies anti Aβ. Severe degree of cerebral amyloid angiopathy with extensive amyloid deposits in the vessel walls according to Vonsattel's scale was seen. Both medium and small-sized leptomeningeal and cortical vessels were affected. The sporadic form of CAA was diagnosed. In our opinion CAA can have an influence on hemorrhagic transformation in ischemic stroke in patient treated with rtPA.

Diplomyelia in a patient with clinical suspicion of autosomal recessive spastic ataxia of Chalevoixe-Saguenay type (ARSACS)

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Autosomal recessive spastic ataxia of Charlevoixe-Saguenay (ARSACS) is a distinct form of cerebellar ataxia related to mutations in gene on chromosome 13q12.12 encoding sacsin – a protein involved in chaperon-mediated protein folding. Characteristic clinical features of the disease are ataxia, spasticity, distal muscle wasting with the onset age of 12-18 months, dysarthria, nystagmus, and finger and foot deformities.

We present a case of a 32-years-old man with, progressing from the teenage period, distal muscle atrophy, spastic lower paraparesis with bilateral foot drop, dysarthria, nystagmus, and sensory disturbances in lower limbs. Electrophysiological studies revealed axonal damage to motor fibers and neurogenic record in lower limbs muscles. Brain MRI demonstrating also upper part of the cervical spinal cord (till the level of C3) revealed only cerebellar atrophy, especially in the upper vermis, but MRI scan of the thoracic spinal cord and lower cervical segments (C6-C7) was normal. Basing on these results and clinical picture ARSACS was diagnosed. The patient died suddenly at home a few months after hospitalization. The death was followed by dyspnoe, anartria, loss of sphincter control, and coma.

Brain gross examination showed cerebellar atrophy and brain edema. Gross examination of the spinal cord revealed extraspinal tumor at the level of C4-C5. On microscopic examination the tumor turned out to be an extra spinal cord surrounded by leptomeninges. The additional spinal cord has disturbed intrinsic structure containing clusters of ependymal cells, a few neurons and many pathological vessels. At the level of C4-C5 of the proper spinal cord, double anterior spinal artery was visible, and at the levels of C6 to Th5 it showed ischemic necrosis.

Conclusions: 1) A direct cause of the patient's death seems to be an acute respiratory insufficiency due to thoracic spinal cord ischemia leading to paresis of the intercostal muscles. 2) Diplomyelia does not exclude coexistence of ARSACS because of the occurrence of such clinical symptoms as dysarthria or nystagmus which can not be explained by the presence of spinal cord defect. 3) Since the patient demonstrated also symptoms not characteristic for ARSACS such as sensory disturbances, only genetic examination of the sacsin gene could confirm the clinical diagnosis of ARSASC. 4) Lack of visualization of C4-C5 spinal cord segments in MRI scans prevented diagnosis of diplomyelia *in vivo*.

Analysis of ultrastructural changes in amyotrophic lateral sclerosis

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Introduction: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease with poorly understood etiology and pathogenesis leading to damage to the upper and lower motor neurons at the spinal or bulbar level. The disease causes pathological weakness, muscle paralysis and respiratory failure. Most of the diagnosed cases are sporadic (sALS), and approximately 10% of patients are diagnosed with familial (fALS). The course of the disease regardless of form is the same. ALS is an incurable disease, and the relief of its symptoms is systematic physical rehabilitation.

Material and methods: The samples of muscle biopsy were fixed in 2.5% glutaraldehyde and post-fixed in 1% osmium tetroxide. After dehydration, they were embedded in Spurr. Ultrathin sections were examined with a transmission electron microscope (Opton DPS 109).

Case report: An 61-year old patient was admitted to the Department of Neurology due to a progressive weakness in the upper and lower extremities with diagnosed chronic sensory and motor polyneuropathy (2013). In addition, the patient was diagnosed with degenerative disease of the spine, prostatic hypertrophy, and gastro esophageal reflux. In the last (2016) EMG study, there were features of chronic damage of frontal spinal cord cells at C5-6, C8-Th1, Th9-10, L2-4, L4-5 levels with active denervation process of motor neuron. On the basis of these studies, ALS was suspected. In order to deepen the diagnosis, a skeletal muscle biopsy was performed.

Conclusions: In the skeletal muscle biopsy numerous atrophic muscle fibers have been found. Small diameter and diverse architecture fibers were present, including

multi-nuclear fibers. Hypertrophic fibers, often with large Z-line streaming areas were observed. The cytoplasm of most muscle fibers exhibited numerous degenerative features including pathology of mitochondria, for example poor systems cristae, mitochondrial swelling and the presence of paracrystalline inclusions. Often muscle fibers of different diameters were adjacent to numerous folds of basal membranes. Ultrastructural images indicate the process of chronic denervation.

Expression of Antithrombin III and Tissue Factor in gliomas

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Introduction: Factors involved in control of physiological hemostasis have some functional cross-points with cancerogenesis. Tissue factor (TF) is a basic activator of extrinsic coagulation pathway, being produced by stromal cells and secreted after vessel injury. TF influences also on angiogenesis, apoptosis and endothelium function. Antithrombin 3 (AT3) is the most abundant serum coagulation inhibitor, acting mainly by blocking Xa and thrombin. This glycoprotein is produced in liver and endothelium. The role of coagulation factors in cancer has been analyzed in many type of neoplasia, but brain tumors have not been elaborated well.

Material and methods: Paraffin sections from 92 glioblastoma and 9 diffuse astrocytoma cases were used for tissue microarrays construction. Immunohistochemistry was performed routinely with Abcam monoclonal antibodies Anti- TF (17375) 1 : 50, Anti-AT3 (124259) 1 : 200. The tissue expression was assessed with semiquantitative scale: non-reactive, low (positivity up to 30% of cells), medium (30-60%) and high (positivity above 60% of cells).

Results: TF was detected in 82/92 glioblastoma with heterogenous distribution – mostly surrounding and within necrosis, perivascular regions, and within thrombi. TF located in cytoplasm of neoplastic cells and endothelium, but in processes of reactive astrocytes. 27 low, 40 intermediate, and 25 – high expression was observed. In 4 astrocytomas TF expression was low concerning mainly blood vessels and only some neoplastic ells. AT3 was detected in 85/92 glioblastomas with similar heterogenous distribution, and in endothelial cells of 3 astrocytomas. Glioblastomas showed 20 low, 41 intermediate, and 31 high AT3 expression. TF and AT3 expression intensity was not correlated.

Conclusions: In low grade gliomas TF and AT3 expression is negative or low. Glioblastomas show heterogenous but intense expression of key pro and anti-thrombotic factors. Coagulation factors are involved in thrombosis and necrosis within high grade gliomas.

Warsaw neuropathological protocol assessing the cerebral amyloid angiopathy (CAA)

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Sporadic cerebral amyloid angiopathy (CAA) can be diagnosed in 30% autopsy of the neurologically normal elderly. CAA is mostly asymptomatic but can contribute to dementia, cerebral hemorrhage, brain ischemic damage, Alzheimer's disease (AD), Down syndrome (DS), dementia with Lewy bodies (DLB), Parkinson's disease (PD), Creutzfeldt-Jacob disease (CJD).We have developed a protocol and scoring scheme for the assessment the presence and severity of CAA in post-mortem brain tissue. Our aim was to obtain an objective and the repeatable study protocol which can assess the occurrence of CAA pathology. The Warsaw neuropathological protocol consist of macroscopic and microscoping assessment of CAA. The macroscopic changes contains of type of pathology, such as a hemorrhage, big and small, the presence of perforation to the ventricular system, hemorrhage and perforation to the subarachnoid space, hemorrhagic infarction, big ischemic infarction, cortical atrophy. The microscopic changes are assessing in localization frontal, parietal, temporal, occipital lobes and cerebellum, localization and type of involved vessels – cortical and meningeal, type of involved vessels – arteries, veins and capillary, grade of CAA severity in blood vessels according to Vonsattel scale, number of

involved vessels (summary of all blood vessels in all examined structures) and other pathological changes such as microhemorrhages, small ischemic changes or leucoaraiosis, and senile plaques containing β-amyloid. The protocol has 30 points score and can also serve as a scale of CAA. Extent of the scoring system is maximally 30 points which can be testified as a very advanced CAA process.

Rare central nervous system opportunistic infection in the course of AIDS: autopsy example

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Human immunodeficiency virus (HIV) infections are still an emerging problem. Improved therapeutic strategies resulted in overall decrease in HIV-related mortality. However, opportunistic infections remain a major cause of death in HIV-positive individuals including several CNS conditions such as toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy (PML) or cytomegalovirus infection.

We present a case of 39-year-old man admitted to the neurology department with progressing focal neurological symptoms such as visual, language disturbances, swallowing difficulty, loss of coordination and concentration. Physical examination showed extrapyramidal syndrome, cognitive impairment, dysarthria. MRI revealed numerous T1 hypointense, T2 hyperintensive lesions in white matter without enhancement and mass effect. Laboratory test confirmed HIV infection and PMR examination showed anty-JCV antibodies. The diagnosis of PML was established. Instead of multimodal antiviral therapy administration patient died after 5 months of hospitalization.

Autopsy with neuropathological examination was performed. On gross section multiple bilateral subcortical and deep white matter gray-yellowish focuses and areas were found, mostly in supratentorial area, but also in brainsteam. Microscopic examination demonstrated small subcortical severe active demielinization lesions which expanded into larger areas within white matter in part simulating cerebral infarctions. At the margins numerous swollen oligodendrocytes with enlarge basophilc nuclei with eosinophilic inclusion bodies and bizarre astrocytes with multilobulated hyperchromatic nuclei were present. The inflammatory reaction was low. The picture was characteristic for PML infection. Outside these lesion, there were also microglial nodules with multinucleated cells typical for HIV encephalitis. Moreover, general autopsy revealed CMV infection in lungs, liver and kidney, thyroid aspergillosis, aspiration pneumonia and subacute myocarditis.

Our case is an example of newly recognized terminal patient with AIDS complicated by OUN manifestation in the form of PML coexistent with other systemic opportunistic infections (CMV, aspergillosis). In HIV-infected patients there is necessity of precise neuropathological examination with multiple topographic sections according to actual recommendations.

Neurogenesis in adult human brain

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Adult neurogenesis embraces proliferation and differentiation of progenitor cells, as well as their migration and maturation. In the adult human brain two neurogenic regions, the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of lateral ventricles, have been identified. In the dentate gyrus three types of transcriptionally active cells and in the subventricular zone four types of transcriptionally active cells, including GFAP-positive astrocyte neural stem cells (NSCs), have been differentiated.

The aim of the study was to identify and perform a quantitave analyse the density of neurogenic cells in the study group of patients (mean age 70 ± 6.033) with ischemic stroke and in the control group of patients (mean age 64 ± 6.10.95) free of neuropathologic changes who died suddenly within less than10 min.

In both groups in the hippocampal dentate gyrus, as well as in the subventricular zone of lateral ventricles the presence of single GFAP-positive astrocyte stem cells and the transcriptionally active cells labelled with phosphorylated histone H3Ser-10 (p-Histone H3Ser-10)/neural progenitor cells (NPCs), was observed.

The quantitative analysis of cells with p-Histone H3Ser-10 expression in the hippocampal DG did not reveal significant differences between the study and control groups. However, in the SVZ its showed satatistically significant decrease in the density of transcriptionally active cells in the group of patients with ischemic stroke (p = 0.001, test t). A distinct decrease in the density of transcriptionally active cells, proportional to the length of the patients' hospitalization, was observed.

Hypoxia belongs to pathomechanic factors responsible for ischemic stroke that can induce neurogenesis. However, hypoxia along with ischemia and other factors implicated in ischemic stroke, such as the patient's age or duration of ischemia can have a decisive influence on the decrease in the density of transcriptionally active cells in this pathologic process.

Osmotic Demyelination Syndrom – case report

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Osmotic demyelination syndrome (ODS) is a rare noninflammatory illness of CNS consisting in symmetrical damage to myelin sheaths of nerve fibres within a brain. Here is the case of a 46 year old woman, addicted to alcohol and admitted to regional hospital because of haemorrhage into gastrointestinal tract. During the procedure of admittance to hospital, additional examination proved beside anaemia, hyponatremia (Na 122 mmol/l) and hypokalaemia (K 2,9 mmol/l). The patient had blood transfusion, was administered fluids and had her electrolyte imbalance was corrected. 24 hours after admittance the woman was transferred to a district hospital to have a gastroscopy examination performed – at the moment of transfer the level of potasium was 3,8 mmol/l, and sodium level 148 mmol/l (within 24 h sodium level increased by 26 mmol/l). The patient manifested neurological symptoms: first it was agitation, anxiety, hallucination and disorientation, later appeared dysarthria, dysphagia, esotropia. At the end of her hospitalization the patient was unconscious with flaccid quadriparesis, later became spastic. Focal symptoms were not identified, and there were not pyramidal nor meningeal signs. Cerebro-spinal fluid examination without irregularities. In EEG groups of slow waves. MRI showed hyperintense lesion on T2 and FLAIR symmetrically encompassing both hemispheres of cerebellum, hippocampi and basal ganglia. A single focal of a similar character in the central part of pons. The patient died on 74 day of hospitalization. Diagnosis – toxic encephalopathy.

Due to a suspicion that the death of the woman was caused by an unknown toxic substance a medicolegal autopsy, extended by neuropathological brain examination, was conducted. A microscopic examination, HE staining, showed pale white matter lesion symmetrically in both cerebellum hemispheres, basal ganglia, hippocampi and the central part of pons. In Klüver-Barer staining these areas responded to demyelination. Yamamoto staining showed only parts of myelin fibres, among which a significant number of macrophages was identified (confirmed in immunohistochmistry for CD68). In basal ganglia, on both sides, one could observe loss of cells and proliferation of irregular, hypertrophic astrocytes, some of which resembled morphological form of astroglia – Alzheimer cell type 1. On the basis of clinical data and neuropathological examination with MRI imagining the diagnosis was: Osmotic Demyelination Syndrome.

Spindle cell oncocytoma – clinicopathological characteristics of three very rare pituitary tumors

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Spindle cell oncocytoma (SCO) of adenohypophysis was first described in 2002 by Roncaroli *et al*. It was subsequently recognized as a distinct entity in the 2007 WHO classification of CNS tumors. SCO is very rare, benign neoplasm originating from folliculo-stellate cells of the hypophysis. It usually causes pituitary disfunction and visual disturbance. This rare entity can be confused with other sellar tumors such pituitary adenomas, craniopharyngiomas, schwannomas and pituicytomas. SCO is composed of interlacing fascicles of spindle cells that alternated with areas of epithelioid-like cells that exhibited eosinophilic, granular cytoplasm. Cells are positive

for S-100 protein, vimentin, epithelial membrane antigen (EMA) and thyroid transcription factor-1 (TTF-1) with lack of neuroendocrine and adenohypophysial markers. There are intracytoplasmic accumulations of large mitochondria in electron microscopy. We present 3 cases of SCO in the group of more than 3000 pituitary tumors operated on by one neurosurgeon between 2003-2017. Results. All pts presented pituitary insufficiency and visual disturbance before surgery. There was no diabetes insipidus before surgery. Initial MRI showed pituitary tumors in two pts and craniopharyngioma was suggested in the third case. Two pts underwent radical surgery but huge, invasive tumor was removed incompletely. In the all 3 pts histopathological examination revealed spindle epithelioid cells arranged in interlacing fasciles with abundant eosinophilic cytoplasm and oncocytic features. Mitoses were rarely observed and necrosis was absent. The tumor cells showed coexpression of S100 protein, vimentin, TTF-1 and faint cytoplasmic immunoreaction for EMA, whereas GFAP, chromogranin A and anterior pituitary hormones were negative. Ki-67 was expressed in 1% to 10% of neoplastic cells. Ultrastructurally, irregular and elongated cells exhibited long, interlacing processes. The cytoplasm was packed with abundant mitochondria with lamellar structures. In one case mitochondria were giant with disrupted cristae. There were no neurosecretory granules. No tumor regrowth was observed.

In conclusion:

1. SCO is very rare, benign pituitary tumor causing visual disturbance and pituitary disfunction.

2. Clinicoradiological course of the SCO is similar to nonfunctioning pituitary adenoma.

3. Immunohistochemical and ultrastructural characteristics of SCO are crucial in identification and differential diagnosis with other sellar entities.