

**European Network on Brain Malformations**

**COST ACTION CA16118**  
**2nd Neuro-MIG Training School**

Novi Sad, 14-15 December 2018.

***Pathology of Brain Malformations***



*Institute for Histology and Embryology*

*Institute for Anatomy*

*Faculty of Medicine*

*University of Novi Sad*

*Novi Sad, Serbia*



University of Novi Sad  
Faculty of Medicine Novi Sad

*Publisher*  
Faculty of Medicine Novi Sad  
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*Printing Company*  
SAJNOS, Novi Sad

*Circulation*  
30

CIP – Каталогизacija у публикацији  
Библиотека Матице српске, Нови Сад  
616.8(048.3)

**NEURO-MIG Training School (2 ; 2018 ; Novi Sad)**

Abstract book / 2nd Neuro-MIG Training School [with subject] "Pathology of brain malformations", Novi Sad, 14-15 December 2018. ; [editor-in-chief Rajko M. Jović]. – Novi Sad : Faculty of Medicine, 2018 (Novi Sad : Sajnos). – 58 str. ; 27 cm

Tiraž 50.

ISBN 978-86-7197-560-5

a) Неурологија – Зборници – Апстракти  
COBISS.SR-ID 327126279

ISBN 978-86-7197-560-5  
POSEBNA IZDANJA

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***PATHOLOGY OF BRAIN  
MALFORMATIONS***

*~ abstract book ~*

*Institute for Histology and Embryology*

*Institute for Anatomy*

*Faculty of Medicine,*

*University of Novi Sad*

*Novi Sad, Serbia*

Novi Sad, 2018



## Welcome to Novi Sad

On behalf of the Organizers, we wish you a successful 2<sup>nd</sup> Training School of the COST Action CA116118. The aim of the Training School is to introduce and make familiar trainees with brain sampling technique, biobanking protocols, basic neuropathological stains, and histology of normal and pathological human brain development.

The course is targeted at residents in neuropathology, general pathology, neurology, pediatric neurology, basic neuroscientist, histologist and other specialists in the field are welcome. Residents, PhD students, postdocs and early career investigators (ECI) with research initiative on neuronal migration disorders and other malformations of cortical development are most welcome.

The trainees will have an opportunity to attend short course in grossing of adult and fetal human brain performed by nominated European neuropathologist. The main part of practical session will be based on virtual microscopy technique. It will include computer analysis of high resolution scanned histology slides of neurodevelopmental cases.

The 2<sup>nd</sup> Neuro-MIG Training School aims to theoretical and practical education of young clinicians and scientists in brain sampling technique, normal brain age determination and pathology diagnostic of main brain malformations.

We hope that you will expand your knowledge, get new ideas for future work and enjoy your stay in Novi Sad.



### Training school committee

**Grazia Mancini**, Erasmus University Medical Center, Netherlands, Chair of COST Action

**Hülya Kayserili**, School of Medicine, Koç University, Istanbul, Turkey, Chair of TS committee

**Eleonora Aronica**, Academisch Medisch Centrum, Amsterdam, Netherlands

**Ellen Gelpi**, AKH, Medical University of Vienna, Austria

**Ivan Milenković**, AKH, Medical University of Vienna, Austria

**Marina Kos**, University of Zagreb Medical School, Zagreb, Croatia

### Local Organizing Committee

**Ivan Čapo**, Faculty of Medicine, University of Novi Sad, Serbia, Chair

**Nada Vučković**, Faculty of Medicine, University of Novi Sad, Serbia

**Emilija Manojlović Gačić**, School of Medicine, University of Belgrade, Serbia

**Sanja Milenković**, University Clinical Hospital Center Zemun, Belgrade, Serbia



### CA 16118 Action Summary

Among congenital brain disorders, malformations of cortical development (MCD) are a group of rare diseases, but constitute a major cause of chronic epilepsy and psychomotor disability worldwide. Little is known about the natural history and no curative therapy exists. The etiology is mainly genetic, and rarely environmental or multi-factorial, but diagnosis requires special expertise among neurodevelopmental disorders. The emergence of novel neuroimaging and genomic technologies potentially allows rapid and accurate characterisation and gene discovery, but challenges scientists and clinicians of efficiently interpreting and translating these data for the benefit of patients. In Europe, expertise on MCD is very fragmented and confined to personal interest of a few experts and basic scientists studying cortical development are not always connected with clinicians. This COST Action will, for the first time, bring together clinicians and researchers in the field of brain malformations, to create the interdisciplinary, pan-European Network Neuro-MIG, advancing the understanding of MCD pathophysiology and translating this knowledge to improve the diagnostic and clinical management of the patients. This Action will harmonise MCD classification, based on the advances in genetics and neuroimaging, develop guidelines for clinical management, create best practice diagnostic pathways, coordinate databases from different countries to utilize them for collective research initiatives aimed at developing appropriate therapies, identify common pathophysiological mechanisms through collaborations, educate young clinicians and scientists, and stimulate translational and transnational exchange. This Action will join forces of MCD experts to reduce health care costs and increase the quality of life of the affected individuals and their families.

**Action website:** <https://www.neuro-mig.org/>

**Contact:** [natchemdrugs@gmail.com](mailto:natchemdrugs@gmail.com)



COST is a unique means for European researchers, engineers and scholars to jointly develop their own ideas and new initiatives across all fields of science and technology through trans-European networking of nationally funded research activities.

**Website:** <http://www.cost.eu>

## *Acknowledgements*

We thank the European Cooperation in Science and Technology (COST),  
for support of the COST Action CA 16118 2<sup>nd</sup> Training School,  
Institute of Neurology, Medical University Vienna for donation of scanned autopsy clinical  
cases of brain malformations for the purpose of Training School and Faculty of Medicine,  
University of Novi Sad for kind help with the organization.



## *Programme*

### Friday, December 14<sup>th</sup> 2018

**8:15–9:10** Registration of participants (Institute for Histology and Embryology, Faculty of Medicine, University of Novi Sad)

**9:10–9:15** Welcome Speech Chair of the Local organizing committee: **Ivan Čapo**

### Plenary Session I

**9:15–10:00** **Ivan Čapo (Novi Sad, Serbia):** *From basic to a practical approach of normal cortico-genesis and brain folding*

**10:00–10:45** **Ivan Milenković (Vienna, Austria):** *GABA<sub>A</sub> receptor distribution in normal and pathological brain development*

**10:45–11:30** Coffee and refreshments

### Plenary Session II

**11:30–12:15** **Ellen Gelpi (Vienna, Austria):** *Sampling of brain tissue for diagnosis and research of adult neurodegenerative diseases*

**12:15–13:00** **Nada Vučković (Novi Sad, Serbia):** *Histology diagnostic techniques and pathological classification of brain malformations*

**13:00–14:30** Light lunch

### Practical Session I (**Ellen Gelpi**)

\*Institute for Anatomy

**14:30–15:15** *Adult brain sampling technique Trainers group I / Trainees\**

**15:15–16:00** *Adult brain sampling technique Trainers group II / Trainees\**

**16:00–16:30** Coffee and refreshments

### Practical Session II (**Ellen Gelpi, Ivan Čapo**)

\*\*Institute for Histology and Embryology

**16:30–17:15** *Virtual histology slide analysis – neurodegenerative cases in adult human brain\*\**

**17:15–18:00** *Virtual histology slide analysis – normal fetal human brain\*\**

**20:00–22:00** Gala Dinner (Trainers and Trainees)

Saturday, December 15<sup>th</sup> 2018

Plenary Session III

9:15–10:00 **Eleonora Aronica (Amsterdam, Netherlands)** *Epilepsy associated malformations of cortical development*

10:00–10:45 **Emilija Manojlovic Gačić (Belgrade, Serbia)** *Disorders of brain size and hydrocephalus*

Discussion

10:45–11:30 Coffee and refreshments

Plenary Session IV

11:30–12:15 **Marina Kos (Zagreb, Croatia)** *Postmortem approach to fetal and perinatal CNS analysis*

12:15–13:00 **Sanja Milenković (Belgrade, Serbia)** *Muscular dystrophies: from muscle to brain*

Discussion

13:00–14:30 Light lunch

Practical Session III (**Eleonora Aronica**)

\*Institute for Anatomy

14:30–15:15 *Fetal brain sampling technique (group I) Trainer / Trainees\**

15:15–16:00 *Fetal brain sampling technique (group II) Trainers / Trainees\**

16:00–16:30 Coffee and refreshments

Practical Session IV (**Eleonora Aronica**)

\*\*Institute for Histology and Embryology

16:30–17:15 *Virtual histology slide analysis (cell migration and specification disorders) Trainers/Trainees\*\**

17:15–18:00 *Virtual histology slide analysis (cerebellum, hindbrain, and spinal patterning defects) Trainers/Trainees\*\**

18:00–18:45 *Trainees Case presentation and Evaluation test*

18:45–19:00 *Closing remarks*



**Plenary Sessions Materials  
(in order of presentation)**

**Ivan Čapo**

*Institute for Histology and Embryology  
Faculty of Medicine, University of Novi Sad, Serbia  
ivan.capo@mf.uns.ac.rs*



**Date of Birth:** 29.05.1984.

**Education**

**Faculty:** 2003-2010. Faculty of Medicine, University of Novi Sad, Serbia

**Internship:** 2010-2011. Novi Sad

**Specialization:**

2015–present Resident in clinical pathology

**Employment:**

2010–present *Institute for Histology and Embryology, Faculty of Medicine, University of Novi Sad*

**Postgraduate study:**

2010. Doctoral thesis (PhD): Faculty of Medicine, University of Novi Sad.

**Academic position:**

2010–2016, Teaching assistant Institute for Histology and Embryology

2016–present Assistant professor/Head of Institute for Histology and Embryology

2017– Head of the Department for Scientific Research Development of Center for Medical-Pharmaceutical Research and Quality Control, Faculty of Medicine, University of Novi Sad

**Membership:**

Serbian Neuroscience Society

Serbian Medical Society – Medical Society of Vojvodina

Serbian Association of Histologist and Embryologist

Serbian Association of Pathologists

European Society of Pathology

European Society for Comparative Endocrinology

**Publications:**

>20 articles as first-, co- or corresponding author;

His main interest are the experimental pathology and developmental neuropathology.

## FROM BASIC TO A PRACTICAL APPROACH OF NORMAL CORTICOGENESIS AND BRAIN FOLDING

*Ivan Čapo*

Development of human central nervous system (CNS) consists of a series of sequential morphogenetic transformations which includes proliferation, migration and differentiation of neurons and glia cells followed by process of synaptogenesis and myelination. The first event in development is the *proliferation of the precursor cells* of neurons and neuroglia. They form a specialized germinal matrix or neuroepithelium (NEP) which is initially flat, but very quickly folds and fuses forming the fluid filled neural tube caudally and the brain ventricles rostrally.

Next event, *neurogenesis*, include a progressive differentiation of many NEP precursor cells into postmitotic neurons. This process comes simultaneously with complex process is *neuronal migration* in which the young neurons leave NEP using specialized radial glial cell (RGC). At the same time some of precursor cells migrate from the NEP and form secondary (subventricular or subpial) germinal matrices, which retain their proliferative potential and multiply in the maturing or mature brain parenchyma as supporting glial cells. All migrated neurons will pass true four steps of neuronal differentiation which include *axogenesis*, *dendritogenesis*, *synaptogenesis*, and *myelogenesis*.

On the other hand, simultaneously to microscopic changes macroscopically, the human brain surface changes from a smooth lissencephalic structure to one that is highly convoluted. This highly complicated process is in cerebral cortex termed as gyrification and in cerebellar cortex called folliation. As a result cerebral brain undergoes changes in surface morphology to create sulcy and gyri or folliae in cerebellum.

Considering the complexity and highly dynamic process of the normal brain development, the basic knowledge about normal microscopic and macroscopic essentials aspect is a obligatory for a proper diagnosis of a brain malformations.

***Ivan Milenković***

*Department of Neurology  
Medical University of Vienna, Vienna, Austria  
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**Ivan Milenković** currently works as neurologist in training at the Department of Neurology at the Medical University of Vienna (MUV), Vienna, Austria. He obtained his doctorate at the Medical University of Vienna 2014 after studying medicine at the Medical Faculty in Novi Sad, Serbia and at the Medical University of Vienna. After graduating he joined Group of Prof. Gabor Kovacs at the Institute of Neurology (Neuropathology) at the MUV where he worked on brain development and ageing. He joined then the residence program at the Department of Neurology, MUV. He is part of movement disorder unit, where he particularly takes care of patients with complex (neuro)metabolic and developmental disorders as well as complex and rare movement disorders.

## ***GABA<sub>A</sub> RECEPTOR DISTRIBUTION IN NORMAL AND PATHOLOGICAL BRAIN DEVELOPMENT***

***Ivan Milenković***

Gamma-aminobutyric acid (GABA) A receptors (GABA<sub>A</sub>Rs) are the major inhibitory neurotransmitter receptors in the adult mammalian brain. They are pentameric chloride ion channels, that can be formed from 19 different subunits (α1-6, β1-3, γ1-3, δ, ε, ρ, σ, τ1-3). The subunit composition of the receptor determines its function, location and pharmacology. GABA<sub>A</sub>Rs are targets of many clinically relevant compounds, including benzodiazepines, barbiturates, ethanol, anesthetics, as well as endogenous modulators such as endozepines and neurosteroids. The majority of GABA<sub>A</sub> receptors is composed of two alpha, two beta and one gamma subunit. The γ2 subunit containing receptors are predominantly synaptic and harbor benzodiazepine-binding site, whereas the δ subunit containing receptors seem to be predominantly extrasynaptic. Synaptically located GABA<sub>A</sub> receptors are responsible for phasic inhibition, whereas the extrasynaptic receptors exhibit tonic inhibition upon the cell. A disruption of the inhibitory GABAergic control results in various pathologic states, including epilepsy, anxiety and depression, ataxia and neurodevelopmental disorders. In the developing brain, however, GABA<sub>A</sub>Rs mediate excitatory actions due to an increased chloride concentration within neurons and seem to control cell proliferation, migration, differentiation, synapse maturation, and cell death. Recent data suggest development-specific expression patterns of GABA<sub>A</sub> R subunits, which change during development. The newest data on expression and function of different GABA<sub>A</sub> receptor subunits during development, as well as changes during neurodevelopmental disorders (i.e. Down syndrome) will be presented.

## Ellen Gelpi

*Institute of Neurology,  
Medical University of Vienna, Vienna, Austria  
ellen.gelpimantius@meduniwien.ac.at*



Born in Barcelona, Spain, 26<sup>th</sup> November 1969.

### EDUCATION / TRAINING

#### A. Positions:

- 1997–2001** Training in Neurology, Assistant, Hospital Universitari Germans Trias I Pujol, Badalona, Barcelona, Spain
- 2001–2008** Training in Neuropathology, Assistant, Medical University of Vienna, Austria (Director: Professor Herbert Budka)
- 2007–** European examination on Neuropathology, European Fellow of Neuropathology by the European Confederation of Neuropathological Societies ([www.euro-cns.org](http://www.euro-cns.org))
- 2009 to 2017** Neuropathologist at the Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS, person in charge since September 2011
- 2017-current position:** staff Neuropathologist at the Institute of Neurology, Medical University of Vienna, Austria

External advisor, Neurological Tissue Bank of the IDIBAPS Biobank, Barcelona, Spain

#### B. Boards/committees/societies:

- Associated Editor “Clinical Neuropathology”, the official journal of the European Confederation of Neuropathological Societies Euro CNS since 2016
- Editorial Board Member of “Neuropathology and Applied Neurobiology” 2014-2017
- Editorial board member of the section “Euro CNS news” of the Euro CNS ([www.eurocns.org](http://www.eurocns.org))
- Advisory board member of the UK-Dementia Platform
- Advisory board member of the “Institut du Cerveau et de la Moelleepiniere” of the Hospital Pitie Salpetriere, Paris
- Advisory board member of the “Oxford Parkinson Disease Center” OPDC, Oxford, UK

#### Societies

- Sociedad Española de Neurología y Club de Neuropatología
- Societat Catalana de Neurologia / Acedèmia de Ciències Mèdiques
- Österreichische Gesellschaft für Neuropathologie (ÖGN)
- European Confederation of Neuropathological Societies (Euro CNS)
- Brain Net Europe (BNE II)

#### Publications:

>170 articles as first-, co- or corresponding author, several book chapters and overview articles;  
Several teaching activities and book translations.

Her main interest are the neuropathological correlates of neurodegenerative diseases.

## ***SAMPLING OF BRAIN TISSUE FOR DIAGNOSIS AND RESEARCH OF ADULT NEURODEGENERATIVE DISEASES***

***Ellen Gelpi***

The study and collection of postmortem brain tissue has gained importance in the last decades due to global reduction in general autopsy rates and due to the fact that patients with neurological disorders and especially neurodegenerative conditions generally do not die in the hospital. There are several European Initiatives for the longitudinal study of specific neurodegenerative pathologies that include clinical, neuroimaging and biomarker assessments. As for many neurodegenerative diseases definite diagnosis can only be established at postmortem examination, brain donation programs have been established in Europe to respond to this medical, social and scientific demand. In this presentation we will discuss the different possibilities to obtain postmortem brain tissue in a general hospital and in an academic or scientific setting, regulatory aspects, the potential limitations and the basic protocols for an appropriate characterization of neurodegenerative conditions according to internationally consensuated protocols.

**Nada Vučković**

*Department of Pathology, Faculty of Medicine, University of  
Novi Sad, Serbia  
Pathology and Histology Centre, Clinical Centre of Vojvodina,  
Novi Sad, Serbia  
nada.vuckovic@mf.uns.ac.rs*

**Education**

**Faculty:** 1977–1982. Faculty of Medicine, University of Novi Sad, Serbia

**Internship:** 1982–1983. Novi Sad

**Specialization:**

1986–1988. (Pathologist Board Certification 26.11.1988.)

2006. Subspecialization in Clinical pathology

**Employment:**

1984–present Pathology and Histology Centre, Clinical Centre of Vojvodina, Novi Sad, Serbia

1983–present Department of Pathology, Faculty of Medicine, Novi Sad, Serbia

**Postgraduate study:**

1983–1985. Master study University of Novi Sad, Faculty of Medicine, Novi Sad, Master's thesis (master of medical sciences): Estimation of extramedullar haematopoiesis maturity as a criteria of gestation age)

1987. Doctoral thesis (PhD): Histological and histochemical characteristics of local recidivs of primary epidermal tumors), Faculty of Medicine, University of Novi Sad,

1994. International Paediatric Pathology Association (IPPA) Courses: X IPPA Course Palic (Yugoslavia) 1988; XI IPPA Course Humlebaek (Denmark) 1989; XII IPPA Course Les Baume Les Aix (France) 1990; XIII IPPA Course Certoso di Pontigliano (Italy) 1991; XIV IPPA Course Loutraki (Greece) 1992. University of Irvine, California (USA)

**Academic position:**

1983–1994, Teaching assistant

1994–1999, Assistant Professor

1999–2004, Associate Professor

2004–present Full professor

**Membership:** Serbian Medical Society – Medical Society of Vojvodina

Lekarska komora Vojvodine

Serbian Association of Pathologists

Paediatric Pathology Society

European Society of Pathology

Balkan Dermatoscopic Association

Serbian Society for Head and Neck Oncology

## **HISTOLOGY DIAGNOSTIC TECHNIQUES AND PATHOLOGICAL CLASSIFICATION OF BRAIN MALFORMATIONS**

*Nada Vučković*

The importance of central nervous system (CNS) malformations are huge because they could have serious consequences on the quality of life by developing mental retardation, cerebral palsy or other neurological problems. Malformations of the brain occur solitarily or, more frequently, in the setting of multiple birth defects. Various insults occurring in prenatal or perinatal period may interfere with the normal CNS development or cause tissue damage. The timeline of brain development is rather narrow, so the timing of an injury determines the pattern and severity of malformation, with earlier events typically leading to more severe phenotypes. The time of event is even more important than the actual cause. Malformations are still usually of unknown cause, but for some of them genetic changes are found. Various chemicals, infectious agents, ischaemic episodes, as well as environmental factors are important.

The brain development passes through stages which could be grouped according to the major event:

1. Formation of brain structures: 0-20 weeks (with major malformations of neural tube defects: anencephaly; encephalocele; myelocele; holoprosencephaly; agenesis of corpus callosum...)
2. Neuronal migration: 6-20 weeks (with disorders such as: lissencephaly, polymicrogyria, neuronal heterotopia; focal cortical dysplasia...)
3. Cell proliferation and brain growth: 0 weeks-12 years
4. Differentiation, maturation, synaptogenesis: 12 weeks – 12 years
5. Programmed cell death: up to 6 postnatal months
6. Myelination: 13 weeks – 30 years

Careful prenatal ultrasound examination is important if CNS malformations are suspected, but due to developmental changes of the brain it must be correlated with the gestational time. Pathological diagnosis of demised fetus with CNS malformation is usually influenced by the time of fetal intrauterine retention.

## ***Eleonora Aronica***

*Department of (Neuro)Pathology  
Amsterdam University Medical Center  
University of Amsterdam, The Netherlands  
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**Eleonora Aronica** is full professor of Neuropathology at the University of Amsterdam's (UvA) Faculty of Medicine (Amsterdam UMC-UvA). She obtained her doctorate cum laude at the UvA in 1993 after studying medicine at the University of Catania (Italy), where she completed her studies as a neurologist. After receiving a doctorate from the UvA she moved to the USA, where she had research associated appointments in Albany and New York. Subsequently, she moved to The Netherlands and joined the Department of Neuropathology of AMC at the UvA, where she completed the Neuropathology residence program. She leads a research group focused on translational research into Epilepsy and aiming to understand the pathogenesis, epileptogenesis and pharmacoresistance. Her scientific honours include the Michael Prize (2011) for epilepsy research. She has published more than 300 peer-reviewed articles and several book chapters. She is coordinator of the international course of “Developmental Neuropathology” of the European Confederation of Neuropathological Societies/EURO-CNS and member of the ILAE Task Force on *Focal cortical Dysplasia* (FCD), European consortia (FP7, Horizon 2020) and European Network on Brain Malformations COST Action CA16118.

## ***EPILEPSY ASSOCIATED MALFORMATIONS OF CORTICAL DEVELOPMENT***

***Eleonora Aronica***

Epilepsy is one of the most common neurological disorders, affecting about 50 million people world-wide. The disease is characterized by recurrent seizures, which are due to aberrant neuronal networks resulting in synchronous discharges. The recent development of imaging- and epilepsy-surgery techniques is now enabling the identification of structural abnormalities that are part of the epileptic network, and the removal of these lesions may result in control of seizures. Access of this clinically well-characterized neurosurgical material has provided neuropathologists with the opportunity to study a variety of structural brain abnormalities associated with epilepsy, by combining traditional routine histopathological methods with molecular genetics and functional analysis of the resected tissue. This approach has contributed greatly to a better diagnosis and classification of these structural lesions, and has provided important new insights into their pathogenesis and epileptogenesis. In addition to studies on surgical samples, postmortem human brain tissue from subjects with and without epilepsy has become useful for a better understanding of the complex network changes associated with epilepsy. Tuberous Sclerosis Complex (TSC) represents a model disease for investigating mammalian target of rapamycin (mTOR)-related epileptogenesis. The spectrum of developmental malformations related to mTOR dyregulations, ranging from focal cortical dysplasia (FCD) to hemimegalencephaly and megalencephaly, will be presented, discussing challenges related to the implementation of recent genetic data and the need of an integrated multidisciplinary diagnostic approach and further refinements in MCD classification.

## ***Emilija Manojlović Gačić***

*Institute of Pathology,  
School of Medicine, University of Belgrade, Serbia  
emanojlovicgacic@gmail.com*



**Dr Emilija Manojlović Gačić** was born in Belgrade in 1979. Her education was performed on the School of Medicine, University of Belgrade; she graduated in 2004, finished specialization of pathology in 2011 and finished PhD thesis in 2016. Dr Emilija Manojlović Gačić was employed on the Institute of Pathology, School of Medicine, the University of Belgrade as Assistant professor, where she works on the education of students and residents both in Serbian and English languages. Her field of interest is neuropathology. Pathology of the pituitary gland is the area of her special interest, where she performed PhD thesis and published the majority of scientific work. Sub-specialization in the field of the pathology of the pituitary gland was supported by eminent European pathologists in this field, Prof. Jacqueline Trouillas (Lyon, France) and Prof. Olivera Casar-Borota (Uppsala, Sweden).

## **DISORDERS OF BRAIN SIZE AND HYDROCEPHALUS**

*Emilija Manojlović Gačić*

Hydrocephalus is the consequence of an imbalance between production, circulation and resorption of cerebrospinal fluid (CSF), resulting in the increase of net accumulation of CSF within the central nervous system (CNS), especially ventricles. It is one of the most frequent anomalies of CNS. Hydrocephalus develops as a constellation of causes, including gross brain malformations and secondary causes, particularly infections. Aqueduct stenosis is the most frequent cause of congenital hydrocephalus. Contemporary classification of hydrocephalus relies on the combination of data related to the patient, CSF and treatment. Microcephaly is a condition defined as the decrease in brain size and weight below the third centile compared to the corresponding databases. Whilst primary microcephaly is a static developmental anomaly associated with the reduction of neuron production during neurogenesis, secondary microcephaly is the progressive condition which develops after birth, without neurogenesis disruption. The major concern in microcephaly is the intellectual prognosis. The macroscopic recognition of microcephaly is advisable after 26 weeks of gestation, owing to the presence of all primary fissures. Megalencephaly is oversized and overweight (greater than 2.5 standard deviations above the mean) brain, aside from any neurological dysfunction. There are two types of anatomic megalencephaly, hemimegalencephaly (HMEG) and dysplastic megalencephaly (DMEG), both being rare and genetically defined. Since both could be associated with rare syndromes, check for stigmata of syndromic causes is mandatory. Histologically, mild laminar to severe pachygyria mixed with areas of polymicrogyria, leptomeningeal glioneuronal heterotopia and cytologic atypia can be observed.

## **Marina Kos**

*Institute of Pathology, Medical School University of Zagreb  
Clinical Department of Pathology and Cytology “Ljudevit Jurak”  
Clinical Hospital Center “Sestre milosrdnice”, Zagreb, Croatia  
dr.marina.kos2412@gmail.com*



**Marina Kos**, MD. PhD. graduated in medicine from the Medical School University of Zagreb, and trained in pathology in Pula and Zagreb. During her residency she finished postgraduate studies in clinical cytology and defended the master thesis on thyroid pathology. She began working at the Institute of Pathology Medical School University of Zagreb and Clinic for Gynecology and Obstetrics Petrova of the Clinical Hospital Center Zagreb in 1992.

Gynecological, fetal and perinatal pathology became the main fields of her interest, and in 1996. she got PhD degree for the thesis named “Pathological changes of placentas from pregnancies with abnormal Doppler measured blood flow”.

Besides lecturing to undergraduate medical students in Croatian, she became Course Coordinator for Pathology to undergraduate medical studies in English in 2004. and has been lecturing in English ever since. She also lectures at postgraduate studies, doctoral studies and many postgraduate courses.

She published a number of peer reviewed publications, several chapters in international text books and is the first author of the textbook “Placental Pathology Basics” (in Croatian), published in 2011. In 2017. she was awarded the “Ljudevit Jurak Award” for her engagement in comparative veterinary/human pathology.

In 2012 and again in 2016. she was elected president of the Croatian Society of Pathology and Forensic Medicine. She is a member of the Advisory Board of the European Society of Pathology and a member of the Gynaecopathology Working Group of the ESP. Presently, she is employed at the Clinical Department of Pathology and Cytology “Ljudevit Jurak” of the Clinical Hospital Center “Sestre Milosrdnice”, Zagreb and is a full professor of pathology at Medical School University of Zagreb, Croatia.

## **POSTMORTEM APPROACH TO FETAL AND PERINATAL CNS ANALYSIS**

*Marina Kos*

Autopsy is the only way of obtaining fetal and neonatal tissues for further scientific investigations. The cause of CNS damage may be discovered in the placenta, that should always be sent for pathological examination. The CNS autopsy is done as a routine part of postmortem investigation. The gross inspection includes measurement of the head, chest and abdominal circumference and visual inspection of the head and face. Depending on whether CNS and spinal cord malformation is suspected, the scalp can be opened by intermastoid, suboccipital incision or by a question mark shaped incision. The scalp is then reflected anteriorly and posteriorly and calvarium bones are inspected. Ossification is assessed, as well as the sutures and the fontanelles. The fetal skull can be opened following the sutures, while in older babies and young children the method is the same as in the adult. In small fetuses, less than 16 weeks gestational age, opening under water is advised. Surface soft meninges are inspected, the attention focused to possible consequences of trauma during delivery and dural sinuses are examined for possible thrombosis. The surface of the brain has to be assessed by comparison to the expected appearance for age. The brain should be removed from the skull by placing the hand behind the head, this way as the brain falls away from the skull base the cranial nerves, pituitary stalk and tentorium can be inspected and cut across. The spinal canal is also visualized, the scissors are inserted and the spinal cord is cut below the brain stem. Because of the soft consistency, weight in of the brain is usually difficult, especially in small fetuses. It should be done before fixation that should last for at least 1 to 2 weeks. Placing a container near the source of loeheat (radiator) may hasten the fixation. After fixation the brain is sampled and examined microscopically.

## ***Sanja Milenković***

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**Sanja Milenkovic**, Serbia, Associate Professor Sanja M. Milenkovic (1965, Sabac, Serbia), MD, PhD is Associate Director for Education and Science of the University Clinical Hospital Center Zemun, Chief of the Pathology Department, as well as, Chef of National Referent Laboratory for neuromuscular biopsies. In September 2014 she was elected as professor of General and Oral pathology of the Dentistry Faculty Pančevo. She is co/founder of the Neuromuscular disease network (NMD) of the Republic of Serbia, Former president of the Serbian Society of Pathology and a former member of the Advisory Council of the ESP (2010-2018). She is coordinator of the ESP Task Force for Promotion of Pathology. She conducted postgraduate training in neuropathology: for muscle biopsy in Laboratory for muscle biopsy Medical Faculty Vienna (2018) and for brain tumors and neuromuscular disease in “Raymond Escurolle” Groupe hospitalier Pital petriere, Paris (2008). The research interest focuses on neuromuscular diseases and brain tumors. They are oriented towards patient material, development of tissue biobank, national network and include all aspects of tissue evaluation and the application in the practices such as histology, immunohistochemistry, in situ hybridization, molecular methods, etc. She is Editor-in-Chief of Journal “Materia Medica” and member of the Editorial board of the Journal Pathology Discovery. (Co)author of more than 80 peer reviewed articles and several books, as well as chapters in books.

## MUSCULAR DYSTROPHIES: FROM MUSCLE TO BRAIN

*Sanja Milenković*

Muscular dystrophies (MDs) are a clinically, genetically, and biochemically heterogeneous group of disorders that share clinical and dystrophic pathological features on muscle biopsy. Most MDs are inherited disorders, but spontaneous mutations can occur. They are characterised by progressive muscle weakness that affects limb, axial, and facial muscles to a variable degree. In specific forms, other muscles, including respiratory muscles, cardiac smooth muscles, and swallowing muscles, can also be affected. Several MDs show significant involvement of the central nervous system (CNS) in addition to muscle weakness. The most common manifestations of CNS dysfunction are: Mental retardation, Epilepsy, Dementia, Structural brain changes on MRI (lissencephaly, hydrocephalus, atrophy), White matter changes on brain MRI, Involvement of eye (retinitis pigmentosa, optic atrophy, cataract or other anterior or posterior anomalies) and Sensorineural deafness. In order for the skeletal muscle to function properly, it requires intact intracellular structural proteins, sarcolemma, glycoproteins and extracellular matrix. The majority of these proteins seem to be related to structural integrity of the sarcolemma. In some cases, these proteins are important to tissues other than skeletal muscle. This leads to the manifestation of clinical features that involve the cardiac, pulmonary, gastrointestinal and central nervous systems. Some MDs accompany CNS lesions, especially in the congenital muscular dystrophies (CMDs). The CMDs and the congenital myopathies (non-dystrophic myopathies with characteristic histological and histochemical findings) constitute the two most important groups of congenital onset muscle disease. Changes in the CNS are most common in: CMD with primary laminin-211 (merosin) deficiency (MDC1A), Alpha-dystroglycan related Dystrophies, Congenital Disorders of Glycosylation (CDG) with abnormal alpha-dystroglycan glycosylation, Collagen VI and Integrin-related CMD forms (Nesprin) and CMD with cerebellar atrophy. Moreover, CNS involvement has been reported in other muscular dystrophies, such as Duchenne muscular dystrophy and congenital and juvenile DM. The most common pathological changes in the CNS are: abnormal white matter signal (MR), occipital pachy or agyria, ponto-cerebellar atrophy, structural grey matter changes, pachygyria, hypoplastic brain stem, cerebellar abnormalities included cysts, Lissencephaly type II/pachygyria, hydrocephalus, occipital encephalocele, microcephaly and Cerebellar vermis hypoplasia. During the presentation, the focus will be on cases to illustrate the importance of multidisciplinary approach to diagnostics.



**Practical Sessions Materials  
(in order of presentation)**