Euro-CNS

# Society News

**European Confederation of Neuropathological Societies**

Dear Readers,

As reported earlier, Euro-CNS is preparing for several educational events. One of which is the European Training Course "Forensic Neuropathology". The Educational Committee recently decided to continue with the organization of "live" courses. The next course will be held at the University of Edinburgh, Scotland, UK. A detailed description is provided below. The European examination in neuropathology scheduled for May 25 and 26, in Vienna is now full. We will announce the next opportunity to take the examination on the Euro-CNS website in due time. The quiz as prepared by Ingeborg Fischer follows in the end.

Wishing you a wonderful festive season and a happy and healthy New Year!

*With kind regards,*
*The Euro-CNS News*
*Editorial Team*

Euro-CNS

# CME Training Course in Forensic Neuropathology 2023, Edinburgh, Scotland, UK

## General

The CME Course "Forensic Neuropathology", organized for the fourth time, will be held from May 2 – 4, 2023 in Edinburgh, Scotland. As with each Euro-CNS course, it will consist of lectures with an emphasis on teaching, alternating with practical (case work-up and digital microscopy) sessions. This will be the first in-person course where no microscopes will be used, all microscopy being digital.

Unique in Europe, perhaps even in the world, the course shall provide an overview of problems in neuropathology which are relevant in judicial cases. The first part of the course will focus on basic issues in neurotrauma and adult forensic neuropathology, post-mortem radiology, CNS affection by intoxications, and differential diagnostic problems. The second part of the course will address the difficult field of pediatric neurotrauma.

During the course, lectures by international experts will be illustrated by discussions of selected cases. Because forensic neuropathology represents an integral part of the forensic medical investigation, the focus of the course shall expand beyond the main issues in forensic neuropathology.

Last, but not least, the program includes a nice and cosy dinner (included in the fee) at a central location in Edinburgh.

The aim of the course is to provide both clinical neuropathologists and forensic pathologists with tools that enable them to ask the right questions, form correct judgments on the quality of forensic neuropathology investigations, or to help them to perform these investigations. The organizers envision an interactive course, making use of case discussions, quizzes and by inviting participants to bring their own cases (a selection will be made in advance).

The registration fee includes catering during the conference (and the course dinner). It excludes any travel expenses and hotel costs. The fee is 875 Euro for Euro-CNS members, and 975 Euro for non-members. On the second day, the course organization will offer you a (free) dinner in a nice location. A limited number of grants of 550 Euro are available for young trainees in neuropathology (under 35 years).

## Accreditation

CME credits (ECMEC) will be requested from the European Accreditation Council for Continuing Medical Education (EACCME). CME accreditation granted by the UEMS-EACCME® provides a guarantee to participants from all over the world that the content of the CME provided is of a high quality, unbiased and didactic and, for European doctors, that this quality will be recognized in their home country. There is a mutual recognition agreement with the American Medical Association (AMA).

## Course organization

*Forensic Neuropathology Course Coordinators:*
B. Kubat,
Maastricht, the Netherlands
Colin Smith,
Edinburgh, Scotland, UK
Jan Beckervordersandforth,
Maastricht, the Netherlands

*Chairman Educational Committee:*
W.F.A. den Dunnen,
Groningen, the Netherlands

## Course location and accommodation

The course will take place at the University of Edinburgh, Scotland. Once you have registered, you will receive information on accommodation, or if you have any queries prior to registration, please contact the Euro-CNS office at secretariat@euro-cns.com.

## Registrations

Registrations will be accepted until the maximum number of participants has been reached. Upon receipt of your online registration, the Course Secretariat will contact you to confirm availability of a seat, and payment instructions. Your registration is confirmed as soon as your

payment has been received. The cancellation fee is 50 Euro. A replacement may be allowed upon consultation with the Secretariat. No refunds are given after April 1, 2023. If you wish to register/pay after April 1, 2023 this may still be possible, but please contact the Course Secretariat to learn whether we still have seats available.

### Travel grants Euro-CNS

A limited number of grants of 550 Euro is available for young trainees in neuropathology. Preference is given to applicants from Eastern European countries. The deadline for submitting your application is March 1, 2023. If you apply for a grant - please indicate this in the online registration form. There are no separate grant application forms.

### Travel grants International Society of Neuropathology

If you are a trainee in neuropathology in a medium low-income country (and non-European/non-North American), we recommend that you apply for an ISN award that will help with covering the cost of travel and participation. For application details and eligibility please see the ISN website. Please note that the applications for ISN grants are handled and administered by ISN and that you need to register normally for the Euro-CNS course.

### Course location

The course will be held at The John McIntyre Centre, The University of Edinburgh, Scotland, UK.

### Accommodation

Once you have registered you will receive an email from the Euro-CNS office with housing options. If you have any questions before you register, please feel free to contact the office. Edinburgh has a wide range of accommodation available, covering all budgets. Information and registration on: www.euro-cns.org.

Euro-CNS

DFP Literaturstudium

## Clinical Neuropathology Volume 42: 1, 2023 – educational summary by I. Fischer and J.A. Hainfellner

Roberta Galli et al. provide a detailed review of the principles, technical requirements, research applications, and potential clinical implementation of Raman spectroscopy of brain tumors. Raman spectroscopy is an optical technology using lasers in the near infrared range to probe a sample. As the monochromatic light irradiates the sample, it interacts with molecular bonds inside the sample, giving rise to so-called inelastic scattering (Raman scattering), whereby the frequency of the emitted light is altered. The emission spectrum represents the molecular composition of the sample and contains characteristic bands reflecting its composition. Thus, such spectra are "fingerprints" of sample biochemistry. Several studies have shown that Raman spectroscopy of tissue samples ex vivo can differentiate between normal brain and tumor tissues. Furthermore, different tumor types and grades yield different Raman spectra. Furthermore, molecular characteristics such as IDH1 mutation status and 1p/19q-codeletion may be predicted by the Raman spectra of fresh or frozen tissues. In vivo analysis in rodent models demonstrated that brain tumors are detected and delineated by Raman spectroscopy. The implementation of this technology in the intraoperative setting requires optimization of instrumentation, appropriate safety protocols, avoidance of artifacts created by external light sources, and accurate positioning of the probe for measurements. Potential clinical applications include ex vivo analysis of tissue samples to assess resection margins, intraoperative measurements to delineate the tumor during resection and identify the target for biopsy, as well as analysis of liquid samples such as cerebrospinal fluid or serum to detect and identify specific disease processes. Limitations of Raman spectroscopy include the time of measurement for each point of interest (approximately 1 second for a volume of 0.2 $mm^3$) and the development of data processing algorithms. Raman spectra do not allow for high resolution mapping of large tissue areas in situ but rather for analysis of specific points of interests. Data processing is required since the spectra do not allow immediate reading by the physician but need advanced mathematical processing to extract meaningful diagnostic information. The authors point out that research thus far is limited to proof-of-principle studies, and that studies on larger numbers of cases are not available. They conclude that interdisciplinary studies involving spectroscopy specialists and clinicians are required to ensure correct application of the technology as well as careful selection of fields of application.

Ankur Jindal et al. report two autopsy cases of encephalitis in patients with primary immunodeficiency. Case 1 was that of a 2-month-old boy presenting with oral thrush, tachypnea, and pneumonia. His elder male sibling had died at 4 months of age of pneumonia. Laboratory examinations revealed anemia and lymphopenia with 0.79% CD3+ T-cells, 1.04% CD19+ B-cells, and 92.68% CD56+ NK-cells. Next-generation sequencing revealed a pathogenic variant in the *RAG1* gene. Based on these findings, he was thus diagnosed with T-B-NK+ SCID. Initial treatment included antibiotic and antifungal medication and intravenous immunoglobulin. He responded to treatment and was discharged on prophylactic medication, and hematopoietic stem cell transplantation was planned. On follow up, he had worsening pancytopenia, oral and perianal ulcers, elevated C-reactive protein, and elevated transaminases. A CMV DNA-PCR in plasma was positive. One week later, the infant developed lethargy and icterus. At 8 weeks post admission, there was onset of seizures and respiratory distress. An MRI scan showed cerebral atrophy with periventricular white matter changes. The infant died from persistent status epilepticus. On au-

topsy, softening of the central white matter, the corpus callosum, hippocampi, internal capsule, as well as pons and medulla was noted. The ventricular lining appeared irregular and covered with exudates. On microscopy, there was cystic degeneration and pallor of the central white matter, ulceration and focal necrosis of the ependymal lining, and a striking diffuse gemistocytic proliferation throughout the white matter and in the cerebellum. These gemistocytes were often binucleated, and some had characteristic owl-eye inclusions, positive for CMV on immunohistochemistry. There were minimal microglial nodules in cortex, pons, and medulla. Disseminated CMV disease was present in the lungs, gastrointestinal tract, adrenal glands, lymph nodes, spleen, and testes. There was organizing pneumonia with diffuse alveolar damage and early invasive aspergillosis. Based on the clinical history and autopsy findings, the CMV infection in this case was most likely acquired postnatally. The unusual histopathologic features are the exuberant gemistocytic response and the relative paucity of microglial nodules and inflammatory reaction, the latter being explained by the underlying immunodeficiency.

Case 2 was that of an 18-month-old boy with a history of recurrent pneumonia, ear infections, and diarrhea since early infancy. His family history was remarkable for the deaths of 2 maternal uncles and 3 maternal cousins between 6 months and 3 years of age due to infection. On clinical examination, there was global developmental delay, pallor, and pustules on the scalp. Laboratory examinations showed anemia, low CD3+, CD4+, and naïve CD8+ T cells, slightly increased CD8+ memory T cells and senescent T cells, and impaired CD62 ligand shedding. A combined immunodeficiency (such as NEMO deficiency or toll-like receptor pathway defect) was clinically suspected; however, NGS revealed no pathogenic variants of primary immunodeficiency genes. At 2 years of age, he was hospitalized again with fever and seizures for 7 days. Clinically, there was pallor, ecchymosis, hepatomegaly, decreased consciousness, choreoatheoid movements, and hypotonia. Laboratory examinations revealed normal WBC counts and normal CRP. A work-up for infections was negative. An MRI scan showed hemorrhage in both frontal lobes, the right occipital lobe, and the splenium of the corpus callosum, and areas of encephalomalacia in the right hippocampus, left temporal lobe, and brain stem. Empirical treatment with ceftriaxone, acyclovir, and antiepileptic drugs was initiated. However, seizures continued, and he acquired pneumonia and died. On autopsy, there were hemorrhagic infarcts of the right frontal lobe, softening of the cortical ribbon, and hemorrhagic necrosis of the right occipital lobe. On microscopy, there was disruption of the laminar architecture of the cortex, neuronal loss, microglial proliferation as well as rare perivascular lymphocytic cuffing. Characteristic Cowdry type A intranuclear inclusions within neurons, astrocytes, and oligodendrocytes were present. Rare giant cells of the Warthin-Finkeldey type were observed. Immunohistochemistry for measles virus was positive. A final diagnosis of measles inclusion body encephalitis (MIBE) was made. Work-up for other infectious organisms was negative. Extracranially, there was organizing viral pneumonia with diffuse alveolar damage, pseudomembranous colitis, and candida esophagitis. Measles-induced encephalitis may manifest as primary measles encephalitis, acute post-measles encephalitis, MIBE, and subacute sclerosing pan-encephalitis (SSPE), depending upon the host immune response. MIBE commonly occurs in immunodeficient children with an onset of 1 year of after measles infection or vaccination, and has features overlapping with those of SSPE. Both forms of measles-induced encephalitis are characterized by the presence of intranuclear and cytoplasmic inclusions. The probable source of infection in the present case was a vaccine received at 9 months of age. The clinical diagnosis of MIBE may be difficult since the typical morbilliform rash is typically absent in immunodeficient patients, CSF analysis is usually normal, and antibody titers to measles in CSF are low.

Dirar Aldabek et al. report a case of hyphal-like structures reminiscent of *Actinomyces* species in a colloid cyst of the third ventricle. The patient was a 35-year-old woman presenting with altered mental status, anisocoria, meningism, and tetraparesis. Imaging studies showed obstructive hydrocephalus and a cyst at the intraventricular foramen, which was endoscopically resected. Histology revealed a cyst wall of connective tissue partially lined by a single layer of epithelial cells associated with chronic inflammation. On Grocott silver stain, structures suggestive of fungal hyphae were present; however, upon close inspection, the shape of the structures did not exactly match that of *Actinomyces*. Similar cases of hyphal-like structures within gelatinous masses of the third ventricle have been published and initially presumed to represent primary actinomycosis. In 1977, however, histochemical and ultrastructural examination of the composition and structure of these structures demonstrated that they were not fungal hyphae.

Dongjin Sun et al. provide a case report and literature review of spinal cord astroblastoma. Astroblastoma is histologically characterized by perivascular pseudorosettes of radially oriented tumor cells with stout processes and distally located nuclei. A typical, yet inconsistent, feature is perivascular and stromal hyalinization. On a molecular level, alteration of *meningioma 1 (MN1)* gene is an essential diagnostic criterion. This tumor entity commonly occurs in the cerebral hemisphere and is extremely rare in the spinal cord. The case presented is that of a 26-year-old woman initially presenting with numbness and weakness of the lower limbs, progressively worsening over a period of 1 year. On MRI, there was an intra-axial mass at the T5-T6 level, which was resected and diagnosed as astroblastoma. Two years later, she presented with sensory disturbance, incontinence, and difficulty walking. At that time, MRI showed 2 intra-axial masses at the T5-T7 and T12-L1 levels. The tumors were incompletely resected. On mi-

croscopy, there were characteristic astroblastic pseudorosettes around hyalinzed blood vessels. Some tumor cells had rhabdoid or signet-ring-like morphology. Mitotic activity of more than 5/10 HPF was noted. The tumor cells were positive for GFAP, Olig2, vimentin, SSTR2, INI-1, and S-100 protein. Fluorescence in situ hybridization (FISH) with a MN1 break-apart probe revealed 1 fused signal and 1 – 4 isolated MN1 signals/cell in 98% of the cells. Next-generation sequencing and Sanger sequencing demonstrated a MN1-BEND2 fusion. The patient received adjuvant radiochemotherapy. Six months after the second resection, a repeat MRI could not exclude tumor recurrence. Thus far, only 5 other cases of spinal astroblastoma have been reported in the literature. The summary of these cases is provided in a table. The authors point out that the astroblastoma morphology may occur in tumors representing anaplastic pleomorphic xanthoastrocytoma or IDH-wildtype glioblastoma on a molecular level. According to the 2021 WHO Classification of Tumors of the Central Nervous System, no definitive criteria for grading have been established. The authors consider the case presented to be high grade based on histological features.

## Quiz #17 Clinical Neuropathology

Below you will find Clinical Neuropathology Review Quiz #17, carefully compiled by Dr. I. Fischer (Aarau, Switzerland) and Prof J. A. Hainfellner (Wien, Austria). The questions refer to the educational summary (see text above) and the papers of this issue of *Clinical Neuropathology* (Volume 42, No. 1/2023, January/February). We recommend making the quiz online, so that you will see your score and the correct answers right away: **https://www.euro-cns.org/journal/journal-quiz/.**

Euro-CNS

*1. Which of the following is the most common localization of astroblastoma?*

a – Brainstem
b – Berebellum
c – Basal ganglia
d – Cerebral hemispheres
e – Spinal cord

*2. Which of the following genetic alterations is typical for astroblastoma?*

a – H3K27 alteration
b – MN1 alteration
c – YAP1 fusion
d – FOXR2 activation
e – MYCN amplification

*3. Astroblastoma corresponds to which of the following CNS-WHO grades?*

a – Grade 1
b – Grade 2
c – Grade 3
d – Grade 4
e – No CNS-WHO grade has been defined to date

*4. Cowdry Type A inclusion bodies may be seen in which of the following infectious diseases?*

a – HSV
b – VZV
c – Measles
d – All of the above

*5. Which of the following has been reported to occur as a complication of vaccination?*

a – Measles inclusion body encephalitis
b – Rubella encephalitis
c – Subacute sclerosing panencephalitis
d – Herpes encephalitis
e – Tick-borne encephalitis

*6. Which of the following are potential fields of application of Raman spectrocopy?*

a – Intraoperative assessment of resection margins
b – Intraoperative identification of tumor tissue
c – Prediction of molecular alterations based on Raman spectra
d – Screening of biofluids for the presence of certain disease
e – All of the above

*7. Hyphal-like structures mimicking actinomycosis have been reported in which of the following cysts?*

a – Arachnoid cysts
b – Rathke cysts
c – Pars intermedia cysts
d – Colloid cysts
e – Epidermoid cysts

*8. Which of the following immunohistochemical stains is typically positive in astroblastoma?*

a – IDH1
b – BRAF (V600E)
c – NeuN
d – H3K27M
e – GFAP

*Quiz submitted by*
*Ingeborg Fischer,*
*Switzerland*
*reviewed by*
*Johannes A. Hainfellner,*
*Austria*

## Upcoming events

XX International Congress of Neuropathology
September 13 – 16, 2023, Berlin, Germany
www.icn2023.de

# Editorial Team Euro-CNS News

Johannes A. Hainfellner
e-mail: johannes.hainfellner@meduniwien.ac.at

Ilja Huang
e-mail: secretariat@euro-cns.com

Christian Mawrin
e-mail: christian.mawrin@med.ovgu.de

Website: **www.euro-cns.org**

## Council



Euro-CNS