Euro-CNS

# Society News

**European Confederation of Neuropathological Societies**

Dear Readers,

Activity is picking up. We are happy to provide a detailed report on the very successful European Basic Course in Neuropathology (held April 20 – 22, 2022) and the European Examination in Neuropathology (June 2 – 3, 2022). Live Euro-CNS board and council meetings are expected to take place in the fall of this year. Euro-CNS is looking into the options for the next European Congress of Neuropathology (2025) which is expected to be a hybrid event. The call for bids is open. In the meantime, relationships with sister societies are strengthening (FENS, ESP, EAN) and there is more interaction than ever. New as per this Newsletter is the educational summary of the contents of this issue of Clinical Neuropathology. The educational summary is followed by our newest Quiz (which you can also make online via the Euro-CNS website www.euro-cns.org).

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

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## Report on the Euro-CNS "Basic course in neuropathology" (April 20 – 22, 2022)

Summary: The first virtual European basic course in neuropathology was held from April 20 – 22, 2022. It was a 3-day program (09:00 – 16:30 hours) consisting of 6 main sessions: "General neuropathology", "developmental neuropathology and epilepsy", "infectious and inflammatory diseases of the CNS", "neurodegenerative diseases", "muscle pathology and metabolic diseases", and "topics in neuro-oncology". The program consisted of lectures, case discussions, Q&A sessions and also had several polls and quizzes. The course was organized by Prof. Wilfred den Dunnen, Chairman of the Euro-CNS Educational Committee. The speakers were Homa Adle-Biassette (Paris), Eleonora Aronica (Amsterdam), Marianna Bugiani (Amsterdam), David Capper (Berlin), Kristl Claeys (Leuven), Wilfred den Dunnen (Groningen), Christian Hartmann (Hannover), Gabor Kovacs (Toronto), Max Kros (Rotterdam), Colin Smith (Edinburgh), Christine Stadelmann (Göttingen), Werner Stenzel (Berlin), and Maria Thom (London). The course was attended online by 177 participants from all continents. The usual number of attendants for a live event is 50, due to the limitation of microscopes. Top 5 were the Netherlands (25 participants), Australia (15), Sweden (11), Germany (11), and Belgium (10). Most participants attended the live stream and were able to participate in the Q&A, polls, and quizzes. Others watched back the recordings later, which was especially convenient for those in (substantially) different time zones.

CME evaluation/feedback: After the event, the majority of the participants completed an evaluation form after which they received a CME certificate from the European Accreditation Council for Continued Medical Education (EACCME). We would like to share with you some of the feedback. As best aspects of this course multiple things were mentioned, such as: "complete and updated information in the various sessions", live microscopy sessions with questions, the digital case material, the fact that this course was virtual and more people (177) than usual (50) could participate, and that participants were able to interact with faculty (via the chat options). Attention points were that some found that the course was too short; more time per session would have been nice, lack of "live" interaction and social networking, going too much in depth for neurosurgery residents, or being too basic for neuropathology residents. Overall, the evaluation gives a good indication of how difficult it is to cover the broad field of neuropathology and to interest participants from various backgrounds, but in general we would see the goals were reached.

As to the "format" of lectures followed by discussion time and/or a quiz or poll, most found this was satisfactory. As innovative elements in this course, participants mentioned the digitized microscopic case material, the live microscopy discussions, and the interactive polls and quizzes.

Ways the course affects clinical practice: To the question "will the information learnt during the course be implemented in your practice?" almost half answered this would be very much the case, and the other half "somewhat". Several mentioned the methylome profiling in neuro-oncology, integration of immunohistochemistry and molecular workup with other daily neuropath practise, use of transcription factors in pituitary tumors, making more extensive differentials, and more. It would be fair to say that everyone took at least something practical home.

Commercial bias: All faculty members had provided statements concerning any conflicts of interest. No participant could give an example of bias in a presentation during this course. Most agreed that the information provided during the course was free of commercial bias.

Evaluations of the sessions and presenters: On a scale of 1 – 10 with 10 being the best score and 1 the lowest, the 6 sessions were scored between 8.7 and 9. Individual Lectures were scored between 8.4 and 9.1.

Evaluation of case material: Providing digital case material prior to the course was considered extremely useful by the majority of the participants. The quality of the cases presented this way was con-

sidered good by almost 100%. We know from previous physical courses that some participants prefer histological slides and a light microscope. In a virtual course, this was obviously not an option. Furthermore, pathological diagnostics move towards digitization anyway, and younger colleagues are already accustomed to this. Therefore, in future courses, we plan to use digitized case material when renewing case material.

## European Examination in Neuropathology (June 2 – 3, 2022)

The European Examination, which had been postponed from 2020, took place on June 2 and 3, 2022 at the Division of Neuropathology and Neurochemistry (Head: Romana Höftberger), Department of Neurology, Medical University of Vienna. The organizer was Tibor Hortobagyi, as chairman of the Euro-CNS Examination Committee. There were two candidates from the UK and one from Switzerland. The local hosts and examiners were Ellen Gelpi, Romana Höftberger, Johannes Hainfellner, and Herbert Budka. Not all candidates could be accommodated this year and will register for 2023. The candidates who passed the exam will be announced in the next issue and on the Euro-CNS website (register of European Fellows in Neuropathology).

## Call for applications European Congress of Neuropathology 2025

Any Society of Neuropathology affiliated with Euro-CNS and interested in hosting the European Congress of Neuropathology is asked to contact the Euro-CNS office (secretariat@euro-cns.org) for information on the bidding procedure and application forms.

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## Clinical Neuropathology 4/2022 – educational summary by I. Fischer and J.A. Hainfellner

Stephan Frank and Jürgen Hench contribute their expert opinion on diagnostic DNA methylome profiling for unified brain tumor typing as introduced by the new, 5th edition of the WHO CNS tumor classification.

The authors appreciate the manifold advantages of this technology. However, they bring up the following disputable remarks:

- they argue that annotated methylome data should be deposited in central publicly accessible repositories, e.g., hosted by the WHO itself, as this would enhance data reproducibility and would also increase the acceptance of this transformative diagnostic approach in the world;
- they point out that one concern in the neurooncology community is that array-based approaches to methylome profiling will not soon become universally available around the globe. Therefore, the WHO has refrained from recommending methylome profiling as a primary or routine diagnostic procedure. Nevertheless, methylome signatures have been defined as essential criterion for the diagnosis of certain rare, newly defined tumor types. This dilemma may be resolved by nanopore long-read epigenomic sequencing which, due to its short turnaround time even enables intraoperative tumor classification. Nanopore sequencing can be established at negligible capital costs, which in principle allows to employ this technology also in low income countries. However, significant local bioinformatic know-how remains an essential prerequisite for the time being;
- they finally remark that a fraction of tumor methylomes will remain unclassifiable, whatever technology is used.

Altogether, the authors believe that, due to its short hands-on time, nanopore sequencing-based methylome profiling will become part of clinical routine in the near future.

They further believe that the full potential of diagnostic tumor DNA methylome profiling will only unfold when all stakeholders agree on public royalty-free data sharing.

Takahiro Takeda et al. demonstrate the diagnostic utility of central motor conduction time (CMCT) measured by transcranial magnetic stimulation (TMS) in two cases of amyotrophic lateral sclerosis where the patients expired shortly after the test was performed and a correlation with autopsy findings was possible. The first case was that of a 65-year-old woman with a 3-year history of dysarthria, weakness, muscular atrophy of the limbs and tongue, and a positive Babinski sign. She was admitted to the hospital because of worsening dysphagia. Her CMCT was significantly prolonged (14.2 ms versus 8.9 ± 1.0 ms). She died 18 days after TMS. The autopsy revealed neuronal loss, gliosis, and TDP43-positive cytoplasmic inclusions in the cervical anterior horn and hypoglossal nuclei. In the cortex, there was a reduction of large pyramidal neurons, neuronophagia, and a loss of nuclear TDP43 staining. Myelin loss of the lateral funiculus of the spinal cord was also observed. The second case was that of a 77-year-old-woman with a 1-year history of dysarthria and hand weakness. Upon admission to the hospital, atrophy of the tongue and of interosseous muscles of the hands was noted. The Babinski sign was negative. Her CMCT was normal at 7.2 ms. She died 20 days after TMS examination. The autopsy showed moderate neuronal loss and TDP43-positive cytoplasmic inclusions in the anterior horn and hypoglossal nucleus, whereas there was no neuronal loss or neuronophagia in the motor cortex and only very rare nuclear TDP43 staining loss. There was no myelin loss in the lateral funiculus of the spinal cord. From these cases presented, the authors conclude that the measurement of CMCT by TMS is useful for measuring pyramidal tract degeneration in ALS patients.

Elena Basenach et al. report on a sustained therapeutic response to bevacizumab in a patient with mosaic neurofibromatosis type 2 with bilateral vestibular schwannomas, 14 additional intracranial/spinal

schwannomas, and 1 meningioma. The patient had undergone resection of a vestibular schwannoma at the age of 15 years with subsequent hearing loss and facial nerve palsy. Ten years later, he presented with headaches and vertigo, and imaging revealed multiple schwannomas and a meningioma. Three of these tumors were resected. To preserve hearing, the patient was treated with bevacizumab for 2 years. Next-generation sequencing performed on DNA of leukocytes and oral mucosa detected no *NF2*, *SMARCB1*, or *LZTR1* mutation, however the 3 surgically removed tumors each contained a heterozygous c.784C>T p.(Arg242*) *NF2* pathogenic variant. The response to bevacizumab therapy was tracked by volumetric measurements on imaging. The schwannomas showed an annual volume reduction of 9%. The meningioma continued to grow at an average rate of 8% annually under bevacizumab (compared to 363% annually pre-treatment). The authors highlight that the identified *NF2* variant is a frequent variant in de-novo mosaic *NF2* and conclude that the correlation of treatment response with a specific genotype in *NF2* may facilitate treatment decisions.

Monish Maharaj et al. report a case of cerebellar liponeurocytoma with anaplastic features occurring in a 61-year-old man who experienced multiple recurrences of disease. On initial presentation, he had a 2-month history of recurring headaches. MRI revealed a solid and cystic left cerebellar mass of 54 mm maximal diameter, which was subtotally resected. Histology revealed a neurocytic tumor with lipid accumulation in tumor cells with scattered mitotic figures and a Ki67 proliferation index of 8.2%. Three years later, a radiographic tumor recurrence was noted and another resection was performed. At that time, histology revealed readily identifiable features of anaplasia including brisk mitotic activity, necrosis, and microvascular proliferation, with a Ki67 proliferation index of 12 – 15%. The patient then underwent radiation therapy dosed at 60 Gy. Six months later, another radiographic recurrence was seen, and a third resection was performed, including a margin of macroscopically normal brain. Histology was comparable to the previous resection with a Ki67 proliferation index of 5 – 6%. Three years later, the patient remained in remission. The authors point out that, even though multiple recurrences and increased aggressiveness upon recurrence has been documented for this rare tumor type, no consensus treatment recommendations currently exist. They conclude that in the setting of atypical histological features, aggressive resection and adjuvant radiotherapy should be considered.

In their case study, Niklas Abele et al. report on molecular subclones in a meningioma recurring three times over a period of 11 years. *NF2* alterations are frequent in meningiomas and have been shown to be the initial step in the development of these tumors. In addition, several other genetic alterations have been identified over the past few years in meningiomas without *NF2* alterations, involving *AKT1*, *KLF4*, *TRAF7*, *SMO*, and *PIK3CA*. This case report illustrates the molecular evolution of a histologically atypical meningioma WHO grade 2 in a man who first presented at the age of 51 years and underwent primary resection and three subsequent resections of a right frontal meningioma. Next-generation sequencing was performed on tumor material from two different regions for each tumor sample. The initial tumor harbored a *NF2* splice donor mutation in both locations with allele frequencies (AF) of 71% and 76.6% and an additional *PIK3CA* stop variant with an AF of 44.4%. The first and second recurrences harbored the same *NF2* splice donor mutation in both samples with similar AFs, however, no other mutation was found in these recurrences. The third recurrence continued to harbor this *NF2* splice donor mutation, albeit with a lower AF (14.7% and 37.7%), as well as a *SUFU* stop gain variant (6.8%), and two *SMARCE1* splice variants (AF 9% and 11.5%) in sample A and a *SMO* stop gain (AF 11%), *PIK3CA* R4Q mutation (AF 23.5%), *SUFU* D284N (AF 10.1%), a missense *NF2* variant (H95Y) (AF 28.5%), as well as an oncogenic mutation of *PIK3CA* (L1006F) (AF 13.5%) in sample B. The latter mutation is noteworthy, as an activation of the PI3K-AKT-mTOR pathway is usually found in non-*NF2* meningiomas. This raises the question whether the combination of molecular driver pathways may give rise to more aggressive biologic behavior. In this particular case, the authors concede that the additional molecular alterations in the third recurrence may have been caused by prior radiation. Furthermore, it remains unclear whether *NF2* alterations and non-*NF2* alterations coexist in tumor cells, or if these alterations represent distinct tumor subclones. The decrease in allelic frequency of *NF2* alterations in the third recurrence is at least suggestive of a subclone with retained *NF2* function gaining non-*NF2* mutations.

Toshiyuki Enomoto et al. present an unusual case of a pituitary adenoma with intratumoral proliferation of melanocytes. The 71-year-old woman in this case presented with headache and nausea and was found to have a tumor involving the sphenoid sinus, cavernous sinus, clivus, and sella. The tumor was resected, and histological examination revealed a monomorphic tumor with round nuclei arranged in sheets and pseudorosettes, and immunohistochemically positive for ACTH and T-Pit, classified as a silent corticotroph adenoma. Within the tumor, there were abundant pigmented melanocytes staining with Fontana Masson-stain, immunopositive for S-100 and HMB45. The authors thus sought to investigate the cause of this melanocytic proliferation by staining the pituitary adenoma for basic fibroblast growth factor (bFGF) and alpha melanocyte-stimulating hormone (αMSH), since the former has been speculated to be associated with melanocyte colonization in cutaneous metastases of breast cancer, and the latter is produced from ACTH. The tumor cells were partially positive for bFGF and αMSH, whereas tissue of the normal pituitary gland and two other pituitary adenomas used as controls were negative. The authors point out that this is the first case to report melanocyte proliferation in a pituitary adenoma. The expression of αMSH and bFGF in this case may have contributed to the melanocyte proliferation. The authors also remark that bFGF expression in pituitary adenomas has been linked to aggressive clinical behavior,

and that a report of a melanoma developing from silent corticotroph adenoma exists in the literature and thus, careful follow up in such cases is required.

Fatih Canan et al. report a histologically heterogeneous pediatric glioneuronal tumor with a FGFR1::TACC1 fusion occurring in a 3-year-old girl, presenting as a right precentral solid-cystic mass. Shortly after initial presentation, a hematoma within the tumor developed, and it was subsequently subtotally resected. Histological examination revealed oligodendroglia-like cells in sheets admixed with floating neurons suggestive of dysembryoblastic neuroepithelial tumor (DNT), as well as hypercellular areas composed of ovoid neurons and glial cells. There were no Rosenthal fibers, eosinophilic granular bodies (EGB), mitotic figures, or necrosis. Three years after initial resection, radiographic progression of the residual tumor was noted, and a second resection was done. At that time, histology showed nodules of pleomorphic epitheloid glial cells with pericellular reticulin fibers, xanthomatous cells, dysmorphic neurons, EGBs, and areas of desmoplasia (reminiscent of pleomorphic xanthoastrocytoma), as well as small foci of oligodendroglia-like cells with neurocytic differentiation on immunohistochemistry. The mitotic index was increased to 6 mitoses/10 HPF and the Ki67 proliferation index reached 13%. Next-generation sequencing revealed a FGFR1::TACC1 fusion. The patient was without recurrence at 12 months after this resection. The authors discuss the fact that the FGFR1::TACC1 fusion has not been previously reported in conjunction with such diverse histologic glioneuronal features, in particular not in association with histologic features of pleomorphic xanthoastrocytoma. They concede that there is a certain overlap between ganglioglioma, DNT, PXA, and oligodendroglioma; however, the neurocytic tumor component seen in the case presented has not been previously observed in such tumors. The prognostic importance of FGFR1::TACC fusions in CNS tumors has not been determined yet, but this genetic alteration is of particular interest due to the availability of FGFR tyrosine kinase inhibitors.

## Quiz #14 Clinical Neuropathology

Below you will find Clinical Neuropathology Review Quiz #14, carefully compiled by Dr. Ingeborg Fischer (Aarau, Switzerland). The questions refer to the papers and editorial of this issue of *Clinical Neuropathology* (Volume 41, No. 4/2022, July/August). 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/**

*1. Which of the following genes is implicated in the tumorigenesis of meningioma?*

a – *PTCH*
b – *TSC1*
c – *FGFR1*
d – *NF2*
e – *CTNNB1*

*2. Which of the following genetic alterations is known to be associated with more aggressive biological behavior of meningiomas?*

a – *TERT* promoter mutation
b – *TSC2* mutation
c – *NTRK* rearrangement
d – *ROS1* rearrangement
e – *IDH2* mutation

*3. Which of the following is a characteristic histological feature of cerebellar liponeurocytoma?*

a – Chondroid matrix
b – Rosenthal fibers
c – Melanin pigment
d – Lipid accumulation
e – None of the above

*4. Which of the following tissues normally contains melanocytes?*

a – Epidermis
b – Oral mucosa
c – Respiratory mucosa
d – Leptomeninges
e – All of the above

*5. Which of the following immunohistochemical stains is usually negative in melanocytes?*

a – Desmin
b – S-100
c – SOX10
d – HMB-45
e – Melan A

*6. Which of the following immunohistochemical markers may stain intracytoplasmic inclusions in amyotrophic lateral sclerosis?*

a – CAM 5.2
b – TDP43
c – Chromogranin
d – EMA
e – Ki67

*7. Which of the following is a typical presenting symptom in amyotrophic lateral sclerosis?*

a – Dysarthria
b – Tremor
c – Memory loss
d – Rigidity
e – Aphasia

*8. Methylation profiling of CNS tumors may provide key information on which of the following diagnostic aspects?*

a – Tumor type
b – Prognosis
c – MGMT promoter methylation status
d – Clonal relationships between two separate tumors
e – All of the above

*9. Which of the following is the target of bevacizumab?*

a – VEGFR1
b – VEGFR2
c – VEGF-A
d – Tie-1
e – CXCR4

*10. Which of the following tumors has been reported to harbor a FGFR1::TACC fusion?*

a – Pilocytic astrocytoma
b – Pilomyxoid astrocytoma
c – Dysembryoblastic neuro-epithelial tumor
d – Extraventricular neurocytoma
e – All of the above

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

## Upcoming events

8th Congress of the European Academy of Neurology (EAN)
June 25 – 28, 2022, Vienna, Austria
https://www.ean.org/congress2022

FENS Forum 2022
July 9 – 13, 2022, Paris, France
https://www.fens.org/meetings/fens-forum

34th European Congress of Pathology
September 3 – 7, 2022, Basel, Switzerland
www.esp-congress.org

XX International Congress of Neuropathology
September 13 – 26, 2023, Berlin, Germany
www.icn2023.de

European Association of Neuro-Oncology 2022 (EANO 2022)
September 15 – 18, 2022, Vienna, Austria
https://www.eano.eu/eano2022/

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