Society News

European Confederation of Neuropathological Societies

Dear Readers,

Euro-CNS is planning several educational activities for 2023 and beyond. There will be the next examination in Neuropathology on May 25 and 26, 2023 (Vienna), the Educational Committee is working on the schedule for updated CME courses in neuropathology, and we are preparing for the European Congress of Neuropathology in 2025. In the meantime, Euro-CNS participated in several well-attended neuropathology sessions during the European Congress of Pathology in Basel from September 3 – 7, 2022 (hybrid). Last but not least, the Executive and Council meetings of Euro-CNS were held in Rotterdam (hybrid) and a condensed report follows below. The Educational Committee consisting of the course coordinators also had a planning meeting for the CME courses; we hope to make the next course announcement soon.

The educational summary of this issue of Clinical Neuropathology is provided by I. Fischer and J.A. Hainfellner. The well-known Quiz follows at the end of this issue.

With kind regards,
The Euro-CNS News
Editorial Team

Report on the Euro-CNS Council (hybrid) meeting, September 24, 2022

The Euro-CNS Council meeting was held in a hybrid way at the Millennium Tower in Rotterdam, the Netherlands. Councilors who could not attend "in person", were able to join via Zoom. In this way, attendance was still optimal, and most affiliated societies were represented. A condensed report is provided below.

1. Welcome by Martin Lammens, president of Euro-CNS

Martin Lammens welcomed all attendants and opened the meeting.

2. Minutes of last (hybrid) council meeting (Copenhagen October 2021)

The minutes of the last meeting were approved.

3. National/Regional updates by Councilors

The National society representatives each gave a brief update on activities and developments in their society/country.

4. Officers 2022 and beyond

Editor

Martin Lammens reported that Christian Mawrin had started his new position as Editor-in-Chief in July. Johannes Hainfellner was thanked for his very hard work and achievements as Editor-in-Chief for over 12 years. Johannes has made himself available for advice whenever needed.

Vice-President

At the next live Council meeting (at the occasion of the ICN2013 in Berlin, September 2023), the current vice-president (Bjarne Winther Kristensen) will become president. The Executive committee presented its preferred candidate and also asked Councilor for additional nominations which may be sent until the end of December this year.

Secretary-General

Since Christian Mawrin started as Editor-in-Chief of Clinical-Neuropathology, he has two positions. His position as Secretary-General has become available. No suggestions came up at the meeting, but the Executive Committee will work on this.

Treasurer

As Martin Lammens became president last year, the Treasurer's position also became available. The Executive Committee will look for a candidate.

5. Treasurer's report – Martin Lammens

The detailed accounting was presented on screen, and payments of membership dues until and including this year were presented. Most societies are up-to-date until 2021. All societies will receive an updated request for payment including the year 2022. The Council voted unanimously for an increase of the membership dues from 25 to 30 Euro per member. The dues had been 25 Euro per member for the past 15 years and expenses have increased.

6. Editor's report – Johannes Hainfellner and Christian Mawrin

Christian Mawrin reported that he had just started his position as Editor-in-Chief 2 months ago, after intensive training by Johannes. By the end of 2021, he had a physical meeting with the Publisher and Johannes in Munich. They had discussed the development of the journal and discussed several points for improvement. He plans to introduce one or more new features. Euro-CNS-related reviewers are doing fine. Christian asks the attending Councilors to inform him of any potential reviewers and let him know the contact details and specialty field. Social media may be used to inform members and readers of new publications, and also other announcements.

7. Next European Congress of Neuropathology 2025

Currently, the executive board of Euro-CNS is investigating to hold the congress in cooperation with one

of its affiliated societies. Once the application is completed, the Council will be asked to give approval and the congress venue may be announced.

8. Next International Congress of Neuropathology in Berlin, 2023

Christian Mawrin reported that the scientific program is almost ready. There will be special sessions and an educational day as well. Registration and abstract submission will open early next year. The format is "hybrid". The congress is handled by Conventus, the PCO that also handles the meetings of the DGNN. The website is: www.icn2023.de.

9. Euro-CNS Courses

Wilfred den Dunnen reported that the attendance of the Basic Course in Neuropathology (April 2022) had greatly surpassed his expectations. The course usually has a max. capacity of 50, and the courses were always full, with a few persons on the waiting list. The virtual course had 177 participants. The lecturers had been asked to make their sessions interactive (case discussions, quiz, panel discussion, etc.), which had resulted in a very engaging meeting for participants and lecturers alike. Registrants could access the material until 5 months after the meeting. It was striking that after the meeting, even after additional promotion by bulk mail, there were only 7 new registrations. It shows that participating during the "live-stream" is most successful. Registrants from Australasia and the Americas also participated in the live stream, though for a more limited time, and for the rest watched the sessions later "on demand".

A modern e-learning platform is being developed currently, and the plan is to use it for the next event.

10. European Examination in Neuropathology

Tibor Hortobagyi reported that the Examination of 2022 (Vienna) had three candidates. Two of them had passed the exam: the new EFN Eleanna Kara (London, UK) and Neil Papworth (Preston, Lancashire, UK). A detailed report was provided in the previous issue of Euro-CNS News. The next examination is scheduled to take place on May 25 and 26, 2023, again at the Medical University in Vienna which has proven to be an excellent venue. So far, three candidates have been accepted to sit the next exam, and acceptance of one candidate is pending. If promising candidates are not able to cover the examination fee personally they could ask their institutions to support them. If not successful, please contact Euro-CNS to discuss the options.

11. Euro-CNS Fellowship Training Program

There was one candidate right before the COVID-19 period. This was put on hold. We will pick it up from here. This program is always open for new applications.

12. Sister/Partner Societies – Martin Lammens

A. European Society of Pathology (ESP)

European Congress of Pathology 2022

Euro-CNS had been involved with the organization of two joint sessions and three poster sessions involving neuropathology at the European Congress of Pathology (September 3 – 7, Basel/hybrid).

- The 5th edition of the WHO classification of CNS tumors: marching on into the molecular era. A long course organized jointly by Euro-CNS and the Opthalmic Pathology Working Group of the ESP.
- Methylation profiling: (not) a tool for every tumor? A joint symposium organized jointly by Euro-CNS and the Soft Tissue and Bone Pathology Working Group of the ESP.
- Two Poster Sessions Neuropathology, and one Joint Best Poster Session for Cardiovascular Pathology, the History of Pathology and Neuropathology.

B. Business meeting ESP

Martin Lammens and Johannes Hainfellner had attended the virtual (business) meeting with the ESP Education Subcommittee/Working Group Chairs (September 3, 2022) where cooperation between the groups was an important topic.

The next ECP will be held in September 2023 in Dublin, and Euro-CNS has been invited again to consider one or more joint sessions with other working groups. Martin Lammens will provide an update when there is news.

C. FENS

Christian Mawrin reported that he had attended the last FENS governing Council meeting on July 13 at the occasion of the FENS Forum in Paris. Although part of these meetings are about administration (e.g., elections), and neuropathology seems to be under-recognized in the field

Impression of the Euro-CNS course coordinators meeting on October 21, 2022.

of neuroscience, he feels it is important that Euro-CNS continues to network with FENS and other sister societies and stress the importance of neuropathology and training. The next governing council meeting will take place on November 22 and 23 in Brussels, and Martin Lammens will attend both meetings.

D. EAN

Martin Lammens attended on invitation the annual meeting of the European Academy of Neurology in Vienna (June 25 – 28, 2022). In the opening session, Hans Lassman was celebrated for his outstanding merits for neuropathology especially in the field of multiple sclerosis.

E. Euro-CNS input and participation in educational meetings/courses of other societies. A good development?

The attendants reflected on the pros and cons of organizing neuropathology sessions for other groups/ at other congresses. The conclusion was that Euro-CNS should remain visible and contribute to the scientific quality of neuropathology sessions at other meetings.

13. Any other items of interest

None suggested.

14. Next business meetings (Executive, Council):

Live meeting in Berlin, September 2023, at the occasion of the International Congress of Neuropathology. The congress is from September 13 – 17, 2023. The exact date will be communicated a.s.a.p.

Meeting of the Euro-CNS Educational Committee

The Educational Committee of Euro-CNS, chaired by Wilfred den Dunnen, had convened an evaluation and planning meeting with all its course coordinators on October 21 and 22 in Rotterdam, the Netherlands. In 2022, the basic course in neuropathology had been held virtually. After this success, it is expected that future courses will be either hybrid or virtual in order to reach more participants than in an exclusively physical meeting. The course coordinators discussed the themes and topics of the courses, and plans were made for the continuation of the courses. A more detailed report will follow in the next issue of Euro-CNS News.

Clinical Neuropathology 6/2022 – educational summary by I. Fischer and J.A. Hainfellner

Xu J. Chu et al. report two cases of EGR2-related mixed demyelinating and axonal Charcot-Marie-Tooth disease. The *early growth response 2 (EGR2)* gene encodes a transcription factor which regulates genes involved in Schwann cell differentiation and myelination. Pathogenic mutations of *EGR2* are implicated in early-onset congenital hypomyelinating neuropathy, Dejerine-Sottas neuropathy, Charcot-Marie-Tooth (CMT) type 1, and axonal CMT. Patient 1 was a 6 year-old boy who presented with walking difficulties, distal limb weakness, pes cavus, and absent deep tendon reflexes. Clinical examination revealed distal limb weakness. The compound motor action potential (CMAP) was reduced in the ulnar, median, and tibial nerves, and motor nerve conduction velocities (MNCV) were reduced. The amplitude of the sensory nerve action potential was reduced in the median and sural nerves, and the sensory nerve conduction velocity was reduced. Patient 2 was an 11-year-old boy presenting with walking difficulty, difficulty in rising from the floor or climbing stairs, and distal leg wasting since the age of 6. Clinical examination revealed distal limb weakness and sensory impairment, as well as foot drop and nystagmus. Lower limb deep tendon reflexes were absent. On MRI, the lumbosacral plexus appeared tickened. Electrophysiological studies revealed a reduced amplitude of CMAPs and decreased MNCVs in the ulnar and median nerves. Sural nerve biopsies in both patients showed complete absence of large myelinated fibers and reduction in myelinated fiber density, as well as loss of myelinated and unmyelinated fibers. There was an increase in hypomyelinated fibers. Ultrastructrual studies showed onion bulb formation, attenuated myelin, abnormal folding of Myelin sheaths, and neurofilament aggregation in axons. Next generation sequencing showed a heterozygous missense mutation 1234G>A (p.E412K) in the third zinc finger domain of the *ERG2* gene in patient 1. In patient 2, a novel heterozygous missense mutation of 1063G>A (p.D355N) in the first zinc finger domain was detected, predicted to be pathogenic. In conclusion, these two cases expand the phenotypic spectrum of *EGR2*-associated neuropathy.

Wenbo Wang et al. report on a case of primary central nervous system histiocytic sarcoma with a somatic NF2 mutation and provide a literature review of pCNCHS. The patient was a 24-year-old woman with a 1-year-history of numbness of the left face and fingertips and increasing headaches and nausea for 4 days. An MRI showed a 3-cm irregularly enhancing right frontotemporal lesion adjacent to the dura with a dural tail sign and perifocal edema. The lesion was surgically resected. Histological examination revealed a cellular tumor with a sheet-like architecture, composed of mostly epitheloid, round cells and some spindle cells. The tumor cells were pleomorphic with prominent nucleoli, eosinophilic cytoplasm. There were interspersed large, multinucleated cells, and mitotic figures were easily identified. Furthermore, there were areas of necrosis and invasion of tumor cells into CNS parenchyma. On immunohistochemistry, the tumor cells were positive for CD68, CD163, S-100, BRAF(V600E), and PD-L1. There was no expression of pan-cytokeratin, EMA, GFAP; Olig-2, CD1a, Langerin, SSTR2A, CD20, CD79a, CD3, CD38, CD138, CD15, CD30,

CD21, CD23, Alk1, HMB45, or Melan-A. Based on these findings, a diagnosis of primary CNS histiocytic sarcoma was rendered. Next generation sequencing revealed mutations of NF2 (p.R196*), BRAF (p.V600E), PDGFRA (p.V561D), BRCA1 (p.H437Q), and BRCA2 (p.E2343A). The patient died 10 months after diagnosis despite adjuvant radiation and chemotherapy with apatinib and anlotinib.

Primary CNS histiocytic sarcomas are rare, with only 37 cases reported previously. The authors present an overview of cases reported thus far in a table. The median overall survival is 7 months, and radiation and chemotherapy currently represent the treatment of choice. The authors point out that BRAFV600E, PD-L1, and PDGFRA represent therapeutic targets.

Sarah Al Sharie et al. report on a rare case of H3 K27M-mutant diffuse midline glioma with osseus metastases and provide a review of similar cases reported in the literature. The patient was a 19-year-old man presenting with right-sided weakness, headache, and aphasia. The initial suspected diagnosis was meningitis. Two months later, he presented again with headache, back pain, fatigue, and lower limb weakness. At that time, MRI revealed a tumorous lesion of the conus medullaris, diffuse leptomeningeal enhancement, and osseus lesions of the spine and iliac bone. A biopsy of one of the bone lesions revealed a pleomorphic tumor with fibrillary background, positive for GFAP, H3p.K28M, SOX10, p53, Pan CK, Olig2, and S100. NeuN, desmin, myogenin, brachyury, CD20, CD3, CD61, EMA, LIN28, SALL4, and IDH1 were negative. The nuclear INI-1 expression was retained in the tumor cells. A diagnosis of diffuse midline glioma, H3 K27M-altered was thus rendered. The patient then underwent radiotherapy, which could not be completed due to the patient's deteriorating condition. He died 7 months after initial presentation. The authors point out that metastases of gliomas outside of the CNS are exceedingly rare. In particular, only 5 other cases of diffuse midline glioma metastatic to bone have been reported to date. Four of the 6 patients had bone metastases at the time of presentation and the median overall survival was 7 months. The authors conclude that pathologists should be aware of the possibility of a diffuse midline glioma metastatic to the bone and perform appropriate immunohistochemical studies to enable a timely diagnosis in such rare cases.

Yuan Yuan et al. report a case of a distal hereditary neuropathy with a novel mutation in the *alanyl-aminoacyl-tRNA synthetase (AARS)* gene. Alanyl-aminocyl-tRNA synthetase is an enzyme which plays an essential role in protein translation by attaching tRNAs to their cognate amino acids. To date, autosomal dominant *AARS* missense mutations have been described in 12 families affected by clinically heterogeneous axonal neuropathies. The patient in this case had a history of frequent falls since the age of 18 and developed right lower limb weakness in her early 30s immediately after giving birth to her first child. Two years later, she delivered her second child, after which she also developed weakness of the left lower limb. Her symptoms subsequently progressed, and she had difficulty sitting up and walking. Upon physical examination, there was atrophy of the muscles of the legs and pes cavus, and the deep tendon reflexes were decreased. Muscle strength scores were 0 of 5 in the distal lower limb muscles. Electrophysiological examination revealed an absence of compound motor action potential in the peroneal nerve. The compound motor action potentials of the median, ulnar, and tibial nerves were within normal range, and there were normal sensory nerve conduction velocities and sensory nerve action potentials of the median, ulnar, and sural nerves. Molecular genetic analysis revealed a heterozygous mutation in the splice site of the *AARS* gene (c.2177+1G>A). A biopsy from the tibialis anterior muscle showed atrophy of both type 1 and 2 fibers, as well as target fibers. A biopsy of the sural nerve revealed regeneration clusters and thin myelinated fibers. Based on these findings, a diagnosis of distal hereditary motor neuropathy was rendered. The authors provide a summary of clinical manifestations and genetic causes of distal hereditary motor neuropathy.

Chunhui Cao et al. report a case of IgG4-related disease presenting as a spinal epidural pseudotumor. The patient was a 57-year-old woman with unremarkable medical history who presented with back pain. Imaging studies revealed an epidural mass at the T5 level, which was resected. On histology, there was fibrosis with dense lymphoplasmacytic infiltrates, small vessel hyperplasia, and infarction. The lymphoplasmacytic infiltrate was positive for CD79a, CD38, CD138, LCA, CD21, CD23, Mum1, and IgG. There were 50 IgG4-positive cells/HPF and the ratio of IgG4/IgG was greater than 0.1. Stains for Cyclin D1, p16, Langerin, S100, and BRAF were negative. Clonality studies did not reveal a clonal rearrangement of the *TCR* gene. The concentration of serum IgG4 was 0.53 g/L. Further workup did not reveal any infection or malignancy. Treatment with prednisone and leflunomide achieved remission after 3 months. IgG4-RD can involve almost any organ. The characteristic histological features are storiform fibrosis, massive lymphoplasmacytic infiltrate, obliterative phlebitis, elevated IgG4+ plasma cell count in affected tissues (> 50/HPF), and elevated IgG4/IgG ratio. This entity should be considered in the differential diagnosis of a dural-based mass lesion.

Sumit Das reports a case of argyrophilic grain disease pathology (AGD) in a 67-year-old woman. The patient died due to non-neurological causes and had no relevant neurologic history. Neuropathological examination revealed tau-positive neurofbrillary tangles, pretangles and argyrophilic grains in the ambient gyrus and amygdala, tau-positive balloon cells and coiled bodies in the amygdala, as well as rare argyrophilic grains in the CA1 sector of the hippocampus, corresponding to stage 2 of AGD pathology. Of note, no bush-like astrocyted were present. Argyrophilic grain disease occurring before the age of 70 is a relatively rare occurrence. The author points out that pathologists may not routinely search for AGD pathology at autopsy, especially in the absence of a clinical history suspicious for neurodegenerative disease. Thus, this case suggests the need for routine screening of the amygdala with tau immunohistochemistry in patients over the age of 50 in order

to identify cases with AGD pathology which would otherwise be missed. This could further studies of the pathogenesis and genetic mechanisms of AGD.

Quiz #16 Clinical Neuropathology

Below you will find Clinical Neuropathology Review Quiz #16, 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 41, No. 6/2022, November/December). 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 inheritance patterns has not been described in Charcot-Marie-Tooth disease?

a – Autosomal dominant
b – Autosomal recessive
c – X-linked dominant
d – Mitochondrial
e – None of the above

2. Which of the following is not a typical feature of argyrophilic grain disease?

a – Coiled bodies
b – Ballooned neurons
c – Lewy bodies
d – Argyrophilic grains
e – Deposition of hyperphosphorylated tau-protein

3. Which of the following regions of the brain is typically affected first in argyrophilic grain disease?

a – Medial temporal lobe
b – Frontal lobe
c – Basal ganglia
d – Tectum mesencephali
e – Cerebellum

4. Which of the following is a typical feature of IgG-related disease?

a – Storiform fibrosis
b – Lymphoplasmacytic infiltrate
c – Obliterative phlebitis
d – Elevated numbers of IgG4-positive plasma cells
e – All of the above

5. Which of the following immunohistochemical stains is not expected to be positive in lymphoplasmacytic infiltrates in IgG4-related disease?

a – BRAF(V600E)
b – CD79a
c – CD138
d – IgG
e – IgG4

6. Which of the following immunohistochemical stains is typically negative in diffuse midline glioma, H3K27-altered?

a – H3K27M
b – IDH1(R132H)
c – GFAP
d – Olig2
e – S100

7. Which is the most common localization of diffuse midline glioma, H3K27-altered?

a – Vertebral bone
b – Pons
c – Spinal cord
d – Occipital lobe
e – Frontal lobe

8. Which of the following immunohistochemical stains is typically positive in histiocytic sarcoma?

a – Synaptophysin
b – CD21
c – CD163
d – HMB45
e – SSTR2A

9. Which of the following diseases may feature onion bulb formation in nerve biopsies?

a – Charcot-Marie-Tooth disease
b – Dejerine-Sottas disease
c – Chronic inflammatory demyelinating polyneuropathy
d – Diabetic neuropathy
e – All of the above

10. Aminoacyl-tRNA synthetase binds which of the following nucleic acids?

a – tRNA
b – mRNA
c – siRNA
d – rRNA
e – All of the above

Quiz submitted by
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Upcoming events

XX International Congress of Neuropathology
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www.icn2023.de

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