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Meeting Summary

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Meeting Abstracts

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The French Society of Neuropathology was created in 1989, succeeding the French Club of Neuropathology set up in 1965.

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Free Neuropathol 6:2:2

Meeting Abstract

Cerebrospinal fluid processing in cytology and pathology laboratories: changes of practice

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The handling and analysis of cerebrospinal fluid (CSF) in cytology and pathology laboratories require safety measures, due to the potential risk of infection. The 2004 French safety regulations recommended that the CSF of patients suspected of having Creutzfeldt-Jakob disease was subject to maximum precautions, generally implemented in specialized laboratories. Since 2020, following accidental occupational contamination in research laboratories, new procedures are being developed. In November 2021, the UK's Advisory Committee for Dangerous Pathogens revised its guidance and considers CSF to be a low-risk biofluid, allowing it to be handled with only general laboratory hygiene and safety rules.

Based on UK guidelines, we have updated our CSF handling procedure with a single circuit applicable to all clinical situations and achievable in all laboratories, bearing in mind that any patient who develops cognitive disorders, suspected of suffering from a neurodegenerative disease, must be considered as being at risk of prion disease.

Free Neuropathol 6:2:3

Meeting Abstract

Neuropathological analysis of an ALS patient carrying a *SOD1* missense mutation and a *C9orf72* repeat expansion

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Mutations in the *SOD1* and *C9orf72* genes are responsible for around 10 % of apparently sporadic cases of Amyotrophic Lateral Sclerosis (ALS). We report the case of a-63-year-old man, with no family history of ALS, carrying both a p.Thr55Ile mutation in the *SOD1* gene and a *C9orf72* repeat expansion. He died 15 months after developing gait disturbances. Post-mortem examination confirmed typical features of ALS, including severe loss of spinal and medullar motor neurons. Cerebral atrophy was mild, with preservation of Betz cells. In addition to the widespread TDP-43-positive neuronal cytoplasmic inclusions (NCI), p62-positive TDP-43-negative numerous NCI were found in the cerebellar granule cells. Abundant poly-GA-positive inclusions were observed in the cerebellum, neocortex and hippocampus. This neuropathology was typical of *C9orf72* repeat expansion. SOD1 immunochemistry showed axonal-sprouting but no NCI in motor neurons. Gene therapy targeting *SOD1* may not be beneficial to such SOD1 patients deprived of typical SOD1-positive NCI.

Free Neuropathol 6:2:4

Meeting Abstract

Polyradiculoneuritis with central nervous system involvement: contribution of unbiased metagenomics to the diagnosis

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A 69-year-old male died of rapidly progressing polyradiculoneuritis involving the central nervous system. Symptoms had begun three weeks earlier, with asthenia, diarrhea and weight loss.

Post mortem examination revealed cerebral edema, soft consistency of the cerebellum, necrosis of the midbrain and atrophy of the gray matter of the spinal cord. Microscopic evaluation revealed necrosis in the anterior horns, the cerebellum, brainstem and temporal lobe, associated with severe neuronal loss. In the cerebellum, marked neuronal loss was observed in the Purkinje cell layer and in the dentate nucleus. Microglial activation associated with T-lymphocyte (CD3+) infiltration with foci of neuronophagy and microglial nodules were observed in the most affected regions. In peripheral nerves, perivascular inflammatory infiltrates were seen in the endoneurium and perineurium. No cytopathogenic effects were observed. Anti-rabies antibodies were negative. Unbiased metagenomic analysis revealed the presence of a virus previously unknown in human encephalitis.

Free Neuropathol 6:2:5

Meeting Abstract

Cytoskeleton perturbation in a large spastic ataxia family

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Hereditary spastic ataxias are a clinically diverse group of neurodegenerative disorders, primarily characterized by spasticity in the lower limbs and generalized ataxia. Here, we report an extensive neuropathological and functional study on a large family affected by autosomal dominant spastic ataxia. The disease manifests around the age of 40, beginning with intermittent dystonia in the lower limbs, followed by severe, disabling cerebellar ataxia and spasticity. The condition progresses rapidly, leading to death within 15 years of the onset age. Postmortem neuropathological analysis revealed Purkinje cell loss, motor tract atrophy, and abnormalities in the motile cilia at the ependymal border. Despite these findings, the underlying molecular mechanisms remain unclear. Through a combination of transcriptomic and cellular analyses, we identified significant involvement of cytoskeletal pathways involved in the organization of actin and microtubule networks, which must be related to the molecular cause of the disease.

Free Neuropathol 6:2:6

Meeting Abstract

RNA quality in postmortem brain tissue. The Neuro-CEB experience.

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Molecular research is often carried out on postmortem brain tissue, whose usability must be guaranteed. Brain pH is a good indicator of RNA quality (RIN). However, the procedure is time consuming. Ogata et al (1986) showed that the severity of autolysis of the cerebellar granular layer (ACGL) correlates significantly with brain pH and RIN. Our aim was: **a)** to evaluate this correlation within the Neuro-CEB brain bank cohort, **b)** to extend the study to frequently requested brain regions other than the cerebellum.

We analyzed the RIN in six different brain regions (cerebellum, frontal cortex, temporal cortex, hippocampus, caudate nucleus and *substantia nigra*) from 20 Neuro-CEB postmortem cases: ACGL grade 0 (n = 10) and ACGL grade 4 (n = 10). Our results indicate: **a)** ACGL tend to correlate with the RIN in the cerebellum, but not in the other brain regions, **b)** there is a different susceptibility to RNA degradation in distinct brain regions.

Free Neuropathol 6:2:7–8

Meeting Abstract

AI-driven digital pathology for precision medicine in primary CNS lymphoma

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Primary Central Nervous System Lymphoma (PCNSL) is an aggressive subtype of large B-cell lymphoma (LBCL) with poor prognosis. We developed a novel digital pathology approach to classify PCNSL, detect MYD88 L265P mutations, and predict outcomes using hematoxylin-eosin (H&E) and immunohistochemistry (IHC) samples. Utilizing datasets from over 400 patients, our deep learning models achieved a median AUROC of 0.9 [IQR 0.85–0.93] in categorizing PCNSL molecular clusters. Spatial transcriptomics and single-cell RNA sequencing revealed significant intra-tumoral heterogeneity. Additionally, partial least squares (PLS) Cox models integrating

cell radiomics and clinical features achieved a C-index above 0.9 across datasets. Remarkably, molecular group classifications derived from multi-omics data were accurately replicated using H&E samples alone. These findings demonstrate the potential of artificial intelligence to streamline the clinical implementation of precision medicine for LBCL and PCNSL, enabling more effective and tailored therapeutic strategies.

Free Neuropathol 6:2:9–10

Meeting Abstract

Disease-defining catalytically inactive protein kinase C alpha mutation is a driver in chordoid glioma by pathway rewiring

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Chordoid glioma (ChG) is a rare low-grade brain tumor, characterized by a novel recurrent point mutation, D463H, in the kinase domain of protein kinase C alpha (PKCα). The mutation is always at this position and always to His suggesting it endows a unique function beyond catalytic inactivation associated with other cancer-associated mutations in PKCα. Here we use *in vitro* and *in cellulo* activity assays to show that D463H is not only catalytically inactive but is dominant negative over endogenous PKCs and has a rewired interactome. Specifically, phosphoproteomic, proximity-driven biotinylation, and co-immunoprecipitation mass spectrometry data from HEK293 cells overexpressing $PKC\alpha_{D463H}$ identify altered phosphorylation of substrates and binding to multiple proteins involved in cell-cell junctions that WT enzyme does not interact with. Lastly, single nuclei RNAseq reveals that ChGs derive from specialized tanycytes. Our data suggest that this fully penetrant mutation promotes aberrant interaction with unnatural partners to impair cell junction function.

Free Neuropathol 6:2:11–12

Meeting Abstract

Deciphering genetic and epigenetic of high grade gliomas with BRAF activating alteration is supporting the discovery of a new intracranial MPNST BRAF positive tumor type

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BRAF mutant high-grade gliomas encompasses PXA WHO grade 3, GBM *IDH* WT and HGAP. They share many histomolecular features making differential diagnosis difficult. DNA methylation profiling is useful but some tumors fail to fall in any Methylation Class (MC).

We describe a cohort of 16 intracranial *BRAF*-altered tumors with histological signs of malignancy. Clinico-radiological, morphological, genetic, epigenetic and trancriptomic features are comprehensively described. If already known concomitant molecular alterations were frequently encountered, methylation profiles seems more diverse than expected. Indeed, 2 cases were assigned to the MPNST MC. These cases clustered in a combined t-SNE mixing CNS and sarcoma MC in a separate group of high-grade gliomas located in the vicinity of the MPNST-like cluster. Transcriptomic data of these tumors also showed differences. These data suggest the existence of an intracranial tumor type epigenetically and transcriptonomically close to MPNST whose frequency and prognosis should be clarified in larger series.

Free Neuropathol 6:2:13

Meeting Abstract

High level of *CDKN2A* homozygous deletion discrepancies between fluorescent *in situ* hybridization and DNA methylation-derived copy number in a *BRAF*-mutant glioma cohort - how to solve the dilemma?

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Clarifying the diagnosis and prognosis of *BRAF*-mutant gliomas requires testing for *CDKN2A* homozygous deletion (HD). We herein compare the performances of 5 different techniques currently available to detect it on a retrospective cohort of 20 *BRAF*-altered gliomas, including FISH and DNA methylation-derived CNV. A high level of *CDKN2A* HD detection discrepancy was observed, especially between FISH and other techniques suggesting low sensitivity of FISH. To solve the dilemma, an original approach using genomic alignment of DNA methylation-derived CNV raw data was performed. This revealed a high rate of isolated *CDKN2A* HD excluding *MTAP* among FISH false negative cases, owing to non-specific hybridization of the probe, which is a very commonly used probe targeting the entire 9p21 region including *CDKN2A* and *MTAP*. We therefore report a molecular proof of a previously suspected low sensitivity of FISH assay among *BRAF*-altered gliomas with an original bioinformatic pipeline based on DNA methylation raw data.

Free Neuropathol 6:2:14

Meeting Abstract

FGFR1 wild-type rosette-forming glioneuronal tumours

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We report three cases of rosette-forming glioneuronal tumours (RGNT), diagnosed through DNA-methylation profiling, without the classical *FGFR1* alteration commonly reported in this entity. Desirable criteria include the presence of a *FGFR1* mutation with coexisting *PIK3CA* and / or *NF1* mutation. Several teams have reported the constant presence of *FGFR1* mutation in their RGNT series, suggesting that this criterion should appear as essential in the next classification. Nevertheless, our three cases of RGNT show that the absence of *FGFR1* alteration does not eliminate this diagnosis.

Our finding is also important from a therapeutic point of view since two of our cases have genetic alterations likely to be treated by targeted therapy: *AKT2* E17K mutation by AKT inhibitors currently involved in clinical trials and *KIFF5::ERBB4* fusion by second-generation pan-ErbB tyrosine kinase inhibitors.

Free Neuropathol 6:2:15

Meeting Abstract

Cerebral inflammation in a patient with Kabuki syndrome

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Here we report a 35-year-old man with common variable immunodeficiency (CVID) who presented after a seizure. He had undergone surgery for a congenital heart defect at the age of seven and had developed splenomegaly, lymphadenopathy, interstitial lung disease and autoimmune cytopenias since the age of 28. Clinical examination revealed subtle facial dysmorphic features but no focal neurological deficits.

Brain magnetic resonance imaging showed a right frontal-insular lesion with contrast enhancement. A biopsy confirmed histological evidence of microgranulomatous inflammation.

Polymorphic EBV-positive lymphoproliferation (formerly lymphomatoid granulomatosis) and lymphoma were excluded.

A multigene panel identified a *de novo* pathogenic variant c.7411del p.(Arg2471Aspfs*14) in the *KMT2D* gene associated with Kabuki syndrome.

Cerebral inflammatory lesions are a rare complication of Kabuki syndrome and other genetic conditions associated with CVID, such as CTLA-4 deficiency. Although neuroimaging may suggest demyelinating lesions or neurosarcoidosis, the histologic pattern of T-cell dominant angiocentric infiltrates shares similarities with cerebral lymphocytic vasculitis.

Free Neuropathol 6:2:16

Meeting Abstract

DNA methylation profile in the human hypothalamus: comparison of the profiles of COVID-19, Alzheimer's and control patients

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Introduction: SARS-CoV-2 could be associated with neurological and endocrine symptoms, linked to the infection of the central nervous system, particularly via circumventricular organs, including the median eminence of the hypothalamus. It may also interfere with the progression of Alzheimer's disease. Our objective was to compare the DNA methylation profile of post-mortem hypothalamic tissue from COVID-19 patients with that of controls and of patients who died in the context of Alzheimer's disease.

Methods: We studied the DNA methylation profile of formalin-fixed and frozen hypothalamic tissue from 4 COVID-19 patients, 6 controls, and 6 Alzheimer's patients using Illumina® Infinium MethylationEPI Ctechnology.

Results: The comparison of the CpG methylation profile of COVID-19 patients to controls revealed only 4 differentially methylated sites. In contrast, we observed numerous DNA methylation differences between Alzheimer's patients and both COVID-19 patients and controls.

Conclusion: Our results suggest that hypothalamic epigenetic modifications are more pronounced in Alzheimer's patients than in COVID-19 patients compared to controls, highlighting numerous candidate CpG sites in Alzheimer's patients. The study will continue with **1)** the inclusion of new patients, **2)** a more specific study of CpG islands in gene promoter regions.

Free Neuropathol 6:2:17

Meeting Abstract

Neuropathology of the first experimental transmission of the atypical prionopathy VPSPr (variably protease sensitive) to non-human primate

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Presumed to be the sporadic form of genetic CJD V180I, VPSPr is classically considered as an atypical dementia, incompletely, if any-transmissible in experimental rodent models and often firstly misdiagnosed.

We report here the first transmission of VPSPr in a cynomolgus macaque, 8.5 years after intracerebral inoculation of a brain homogenate from a 75-years-old MV patient.

Neuropathology showed all the elements of the triad, with a specific profile. Notably, immunostaining showed very thin synaptic and neocortical fuzzy deposits of PrP^{d} and biochemistry revealed lower amounts of PrP^{res} than in other prion strains, with a specific ladder-like glycophoretic profile. In addition, we observed unusual massive neocortical Aβ deposits that are absent in mid-aged controls (13.5 years), and different from those observed in two-fold older animals.

Secondary transmission was observed in a limited number of transgenic mice.

The transmission between VPSPr and amyloidosis will be discussed.