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Meeting Summary

63rd Meeting of the French Society of Neuropathology

Meeting Abstracts

December 3rd, 2021

The meeting will take place online at:
https://us02web.zoom.us/s/87471519403

SFNP
SOCIETE FRANCAISE DE NEUROPATHOLOGIE

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

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General assembly (*members only*)

Free Neuropathol 2:32:3

Meeting Abstract

Deciphering the genetic and epigenetic landscape of pediatric bithalamic tumors

Arnault Tauziède-Espariat[1], Marie-Anne Debily[2,3], David Castel[2,4], Jacques Grill[2,4], Stéphanie Puget[5], Alexandre Roux[6], Raphaël Saffroy[7], Guillaume Gauchotte[8], Ellen Wahler[1], Lauren Hasty[1], Fabrice Chrétien[1], Emmanuèle Lechapt[1], Volodia Dangouloff-Ros[9], Nathalie Boddaert[9], Philipp Sievers[10,11#], Pascale Varlet[1#]

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Over the past several years, based on the results of the literature: 1) diffuse midline gliomas (DMG) were defined as a new tumoral type in the 2016 WHO classification, and 2) four different subtypes are now defined depending on their molecular characteristics, and/or locations: DMG H3.3 K27–mutant, DMG H3.1 or H3.2 K27–mutant, DMG H3-wildtype with EZHIP overexpression, and DMG *EGFR*-altered. However, in this rapidly evolving field, a more comprehensive analysis of pediatric bithalamic gliomas is needed. We investigated retrospectively data from 19 pediatric bithalamic gliomas, confirmed by a central radiological review. We also performed a comprehensive clinical, histopathological and molecular evaluation, as well as DNA methylation profiling.

Free Neuropathol 2:32:4

Meeting Abstract

Hedgehog-activated anterior skull base meningiomas over-express GAB1

Julien Boetto[1,2], Julie Lerond[2,3], Matthieu Peyre[2,4,5], Suzanne Tran[5,6], Pauline Marijon[2,4], Michel Kalamarides[2,4,5], Franck Bielle[2,3,5,6,7]

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Anterior skull base meningiomas were previously showed to have mutations activating the hedgehog (Hh) signalling pathway. However, identification of Hh-activated tumours is hampered by the lack of a reliable immunohistochemical marker. We report GAB1 as a potential immunohistochemical marker of Hh-activated meningiomas. GAB1 immunolabeling was compared to SMO mutation detection with Sanger and NGS techniques as well as Hh pathway activation study through mRNA expression level analyses in a discovery set of 110 anterior skull base meningiomas. We showed that a cut-off score of 250 for the GAB1 expression score (from 0 to 400) lead to excellent detection of Hh pathway mutations (sensitivity 100%, specificity 86%). The prospective validation set of 21 meningiomas confirmed the excellent negative predictive value of GAB1 expression score. GAB1 immunohistochemistry is a fast and cost-efficient tool to screen anterior skull base meningiomas and to facilitate the identification of candidate tumours for targeted therapy.

Free Neuropathol 2:32:5

Meeting Abstract

1p deletion and FGFR1 alterations as specific diagnostic tools to discriminate DLGNT from PA in medullary location: an integrative radiological and histomolecular series of 28 cases

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New tumor types such as diffuse leptomeningeal glioneuronal tumors (DLGNT) have been added to the 2016 WHO. Their distinction from others intramedullary gliomas is poorly defined. We retrospectively studied a cohort of 28 children with low-grade intramedullary tumors. The radiological, histopathological and molecular portrait including methylation profiling was established as well oncological treatments data. We observed two main tumor types: DLGNT and pilocytic astrocytomas (PA) that were hardly distinguishable by neuroradiology or histopathology alone. The major criteria to segregate these two tumor types presenting a MAPkinase alteration was the 1p deletion. We observed that these tumors interested different populations (infants for PA, school children for DLGNT). These tumors evolved insidiously during a long period of time, remission was rarely achieved (5/28). Two cases had a deadly evolution. We recommend to systematically assess 1p deletion in intramedullary low-grade glioma. Improving the management of these diseases remains a major challenge.

Free Neuropathol 2:32:6

Meeting Abstract

Classification of pituitary neuroendocrine tumors: Genomic data on cell lineage

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The 2017 World Health Organization (WHO) classification of pituitary adenomas is based on cell lineage and transcription factors (TFs). Transcriptome of 134 PitNETs (RNA sequencing) was used to determine TFs expression at mRNA level, and to provide a canonical transcriptome signature for each cell-types. Pathological study of the present serie of PitNETs included the histological examination and the immunohistochemical tests for all pituitary hormones, proliferation markers and TFs including GATA3.

- Pit1 lineage : based on transcriptome classification, accurate thresholds of immunoexpression for GH, PRL and TSH were established in order to define the different Pit-1 subtypes.

- T-PIT lineage : T-Pit mRNA showed the expected expression in corticotroph PitNETs (35/35), lower in silent ones (Wilcoxon p<10-5).

- Gonadotroph lineage : SF1 mRNA expression showed the expected high expression in gonadotroph PitNETs (29/29), but also in a subset of somatotroph PitNETs (9/21). SF1 immunopositivity was confirmed in this somatotroph subgroup.

Free Neuropathol 2:32:7

Meeting Abstract

Large brain vessel vasculitis in immunocompromised patients

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Inflammation of the large arteries of the brain is a relatively rare condition whose best known mechanism is hyperimmunity with granulomatous reaction or circulating immune complexes. Some vasculitides are secondary to a systemic hyperimmune disease or to an infectious disease (purulent or tuberculous meningitis). We describe here the occurrence of cerebral infarcts in three immunocompromised patients with neutrophilic aseptic meningitis. The MRI appearance was vasculitis of the anterior cerebral arteries (one case) or basilar arteries (two cases). PCR found *Aspergillus fumigatus* in the CSF two days before a positive cavum biopsy in one case. In the other two cases, *Aspergillus fumigatus* was found *postmortem*. The neuropathologic appearance was that of filament-rich necrotizing arteritis. There was no other organ involvement. These observations highlight a probably underestimated cause of central nervous system arteritis whose curability relies on early diagnosis based on repeated and extensive mycological testing in CSF.

Free Neuropathol 2:32:8

Meeting Abstract

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS): a case report

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CANVAS is a rare disease characterized by an intronic biallelic AAGGG expansion in *RFC1*. We report the case of a 74-year-old man who presented with cramps, mixed sensory and cerebellar ataxia, vestibular areflexia and neuropathic pain in addition to parkinsonian symptoms. Macroscopic examination showed atrophy of the cerebellar vermis and pallor and atrophy of the posterior columns. Microscopic examination revealed, in addition to diffuse Lewy body pathology, axonal loss in the dorsal columns and a moderate loss of Purkinje cells in the cerebellum. There was marked astrocytic gliosis in contact with the dendrites in the spinal cord and molecular layer of the cerebellum as well as disorganization of the radial glia in the cerebellum. We report the first complete neuropathological examination of the brain and spinal cord of an *RFC1* patient and describe astrocytic abnormalities that would explain the severe clinical phenotype in the absence of severe neuronal loss.

Free Neuropathol 2:32:9

Meeting Abstract

Neuropathological and amyloid peptide differences between Down syndrome and familial Alzheimer's disease with duplications and missense mutations in APP gene

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Cerebral Amyloid Angiopathy (CAA) is present in 80% of Alzheimer's disease (AD) patients. However, CAA is more prominent in familial cases with APP mutations or duplications (DUPAPP) and in individuals with Down syndrome (DS). In order to explain these differences, we investigated the alterations in the endo-lysosomal pathway, Aβ species and CAA grading in *post-mortem* human brain tissues. Using immunohistochemistry, we identified increased Rab5 puncta size in all cases except those with APP mutations compared to controls. Moreover, we found elevated levels of Aβ40 but not Aβ42 in DUPAPP and in DS correlating with CAA grading. Altogether, these results suggest that CAA arises from specific accumulation of Aβ40 species or, alternatively, that Aβ40 is the principal Aβ species produced in DUPAPP and DS and is more prone to aggregation in blood vessels. The ongoing Aβ and CAA grading analysis aim to unravel pathophysiological mechanisms involved in specific Aβ production and deposits.

Free Neuropathol 2:32:10

Meeting Abstract

Characterization of the endolysosomal compartment of noradrenergic neurons of the *locus cœruleus* in neurodegenerative diseases

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Degeneration of the locus coeruleus (LC) is a common feature in Parkinson's disease (PD), Alzheimer's disease (AD), and Down syndrome (DS). LC is the main source of noradrenaline in the brain, and neuronal loss in this nucleus is associated with dementia. Endolysosomal abnormalities may contribute to the accumulation of toxic proteins. We hypothesize that this could be one mechanism of LC neurons vulnerability (JPND-HEROES, www.heroes-jpnd.eu). Using *post-mortem* paraffin fixed LC of control and pathological cases, we confirm the presence of Aβ plaques and P-tau in AD and DS brains, and Lewy bodies in PD samples. Analysis of confocal microscopy images of immunofluorescence revealed that area of the Rab5 positive puncta of endosomes was increased in AD whereas the area Cathepsin B positive puncta of lysosomes was reduced in PD. Our results suggest that endolysosomal alterations could be a mechanism implicated in the degeneration of noradrenergic neurons, and might be disorder-specific.

Free Neuropathol 2:32:11-12

Meeting Abstract

Neuropathology analysis as a precious tool to ascertain the pathogenicity of nearsplice / intronic variants in Amyotrophic Lateral Sclerosis: example of a SOD1 nearsplice / intronic mutation

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Among etiologic factors assumed to be responsible of Amyotrophic Lateral Sclerosis (ALS), several plausible causative genes have emerged. It becomes crucial to determine the pathogenicity of any genetic variant identified through whole exome/genome sequencing analysis, including those located in non-coding regions. We describe a c.358-10T>G nearsplice/intronic variant in the *SOD1* gene, encoding superoxide dismutase 1, as the second prominent mutation among the SOD1 related-French ALS families. This variant leads to the addition of three amino acids in the protein sequence and impairs the protein secondary structure. Biochemical and neuropathological analyses performed on patient tissue revealed massive cytoplasmic SOD1 and neurofilament accumulation in spinal motor neurons, similar to those observed in spinal cord of patients with D83G or G93D SOD1 mutations. These neuropathology findings ascertain this variant pathogenicity, which is a crucial information in the context of patient enrolment in ongoing clinical trials targeting SOD1 by antisense oligonucleotides.

Free Neuropathol 2:32:13

Meeting Abstract

Implication of microglial cells and peripheral macrophages in Amyotrophic Lateral Sclerosis (ALS)

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In mouse models of Amyotrophic Lateral Sclerosis (ALS), the most common motor neuron (MN) disease of the adult, microglial cells/ macrophages have been shown to participate to disease progression. However, the respective contributions of microglial cells (MG) and peripheral macrophages (PM) were not documented. We have now shown that PM were present around MN axons of ALS patients, both in motor roots and peripheral nerves. In ALS mice, PM were progressively activated and their infiltration into the spinal cord was very limited and disease-length dependent. Transcriptomics analysis showed that MG and PM reacted differently to MN degeneration. Replacing PM by macrophages more neurotrophic, at disease onset, increased ALS mouse survival and downregulated not only PM activation in peripheral nerves but also suppressed proinflammatory responses of MG in the spinal cord, with a switch toward neuronal support. Thus, targeting PM, directly at the periphery, could be of therapeutic value in ALS.

Free Neuropathol 2:32:14

Meeting Abstract

The Neuro-CEB brainbank: a brief history (15 years!) of neuropathology

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The Neuro-CEB national brainbank was founded in 2006 at the initiative of patients' associations, to support a post mortem brain donation program. The missions are to collect, sample, prepare and store nervous tissues (brain and spinal cord), taken post mortem from "control" subjects (not suffering from neurological diseases) and from patients suffering from Alzheimer or Parkinson disease, multiple sclerosis, ataxia, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, or Cadasil. The biological ressources are provided to research teams presenting a suitable project reviewed by a scientific committee. The organization relies on a network of neuropathologists from 14 hospitals. They are in charge of brain sampling and neuropathological diagnosis. The expertise of these neuropathologists ensures a high quality of the samples. Their involvement over the past 15 years alongside research teams, has led to the publication of more than 100 scientific articles. This illustrates the impact of the Neuro-CEB biobank at an international level.

Free Neuropathol 2:32:15

Meeting Abstract

Human Brain Imaging with STochastic Optical Reconstruction Microscopy (STORM)

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The recent development of STochastic Optical Reconstruction Microscopy (STORM) has contributed to major advances in Neuroscience. However this technique is restricted to cultured cells and rodent brain, and no experiment on human samples has been reported so far. To this end, we combined cellular microscopy protocols with neuropathology tissue preparation techniques to characterize physiological and pathological structures in brain samples with 2D-, 3D- and two-color STORM. This approach proved to be particularly effective at visualizing the organization of dense protein inclusions in samples from patients affected with neurodegenerative diseases. These very first results open further gates to a more comprehensive understanding of the human brain organization and revelations about the underlying mechanisms responsible for neurodegenerative disorders.

Free Neuropathol 2, 32:16

Meeting Abstract

AI applied in neuropathology: automated detection of intraepidermal nerve fibers for the diagnosis of small-fiber neuropathies

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The measurement of intra-epidermal nerve fiber density (IENFD) in skin biopsy is the gold standard for the diagnosis of small fiber neuropathy (SFN). This recently described entity causes neuropathic pain and dysautonomia. Numerous etiologies are described, although the majority of them remain idiopathic. The classic DFNIE reading method, derived from a 3mm punch biopsy and 50 micron sections, is based on the anti-PGP9.5 labelling with a visual count related to the analyzed length, a long process thus slowing down its development. Thanks to the digitization of the double-labeled slides in immunofluorescence anti-PGP9.5 and anti-coll IV since 2012 allowing the computer labeling of the traversing fibers, we were able to train an automated reading algorithm which obtains an accuracy of 71% and a recall of 77%.

Free Neuropathol 2:32:17

Meeting Abstract

Histological description of myopathy related to chronic graft versus host disease and characterization of inflammatory infiltrate by imaging mass cytometry

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Chronic graft versus host disease (cGvHD) is a long-term side effect of allogenic hematopoietic cells transplantation, affecting muscles in 3,4 to 7,7% of patients. This study proposes a complete histological and immunohistological description of myopathy in the context of cGvHD and a characterization of the inflammatory infiltrate by imaging mass cytometry technology (IMC). Histological description was performed on 19 patients and divided patients into three groups: 10 patients with no fiber necrosis and no or very low inflammatory infiltrate, 6 patients with fiber necrosis and high inflammatory infiltrate and 3 patients with fasciitis. All patients had variations in fiber size, diffuse MCH-I and perifascicular MCH-II immunostaining. 7 patients were analyzed by IMC. The main inflammatory population was macrophage cells, but eosinophils represented more than 5% of inflammatory cells in 5 cases and seemed to be specific of cGvHD induced myopathy as they were already described in other cGvHD locations.

Free Neuropathol 2:32:18

Meeting Abstract

Highlighting autophagy in a fatal case of Pompe's disease

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Pompe's disease is a rare autosomal recessive disorder caused by mutations in the acid α-glucosidase (*GAA*) gene. Alpha-glucosidase deficit leads to lysosomal and non-lysosomal accumulation of glycogen with different forms of the disease, ranging from early-onset to late-onset form (LOF).

We report the case of a LOF treated by enzyme replacement therapy (ERT), who died of myocardial infarct. We describe expression of several lysosomal and autophagy markers in several tissues. We observed a glycogen-accumulation in brain, associated to increased expression of p62, LC3A/B and LAMP-2 localized in the neocortex and hippocampus. Both neurons and glial cells were affected, however cerebral vessels were normal. Similar results were observed in muscle, heart and liver. Our data suggest that autophagy impairment could be an important pathogenic mechanism in the muscles and the nervous system of patients with Pompe's disease

Free Neuropathol 2:32:19

Meeting Abstract

Diagnosis and classification of peripheral nerve vasculitis: attempt at simplification bases on a retrospective study at Limoges University Hospital between 2014 and 2020

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Peripheral nerve vasculitis remain rare and challenging to diagnose. We tried to simplify criteria of the PNS 2010 by searching for those strongly associated with certain and probable vasculitis, and to propose a management of the biopsy. This retrospective study included 46 patients with definite and probable vasculitis according to the criteria of the PNS 2010 who underwent neuromuscular biopsy and 21 controls (neurolymphomatosis and CIDP). Clinical, biological and pathological features were collected. Criteria discriminating vasculitis from controls were asymmetry, axonal involvement, biological inflammation, T cells in vessel wall, and nerve haemosiderin deposits. Two criteria distinguish definite and probable vasculitis: ovoid and endoneurial haemosiderin deposits. The techniques useful for pathological diagnosis are serial cuts, typing of inflammatory elements and Perls staining. We proposed a slightly simplified classification of vasculitis according to the PNS 2010 and a management of neuromuscular biopsy in this indication.

Free Neuropathol 2:32:20

Meeting Abstract

Experimental evaluation of myosuppressive effects of IFN-gamma

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Dysimmune and Inflammatory Myopathies (DIMs) are acquired idiopathic myopathy associated with immune response dysregulation. Inclusion Body Myositis (IBM), the most common DIMs, is characterized by endomysial infiltrates of cytotoxic T lymphocytes CD8, muscle type II-interferon (IFNγ) signature, and by the lack of response to immunomodulatory therapies. We showed that IBM differs from other myopathies by the presence of chronic degenerative myopathic features including the altered functions of skeletal muscle stem cells. Here, we demonstrated that, in vitro, protracted IFNγ treatment inhibits the activation, proliferation, migration, differentiation, and fusion of myogenic progenitor cells and promotes their senescence through JAK-STAT-dependent activation. JAK-STAT inhibitor, ruxolitinib abrogates the deleterious effects of IFNγ, In conclusion, our results indicate that IFNγ could impair muscle regeneration in the context of inflammatory myopathies and that JAK inhibitors could represent interesting therapies for immune myopathies with IFNγ signature.