Insights From Studies of The Acquired Tauopathies

Daniel P Perl

The Center for Neuroscience and Regenerative Medicine's Brain Tissue Repository, Uniformed Services University of the Health Sciences

Virtually all of the major disorders seen in adults, such as cancer and atherosclerosis leading to myocardial infarction, represent complex interactions between genetic and environmental factors. I will discuss insights gained from studying three examples of acquired (environmental) tauopathies, namely post-encephalitic parkinsonism (PeP), ALS/parkinsonism-dementia complex of Guam (ALS/PDC) and chronic traumatic encephalopathy (CTE). PeP followed a pandemic of encephalitis early in the 20th century, where 50% of affected patients died from the acute illness. A very high percentage of the survivors developed progressive parkinsonism (PeP), characterized by numerous neurofibrillary tangles (NFTs). ALS/PDC occurs among the Chamorro natives of Guam and involves ALS as well as a form of parkinsonism accompanied by progressive dementia (PDC). Affected patients show motor and SNc neuron neurodegeneration with widespread NFT involvement. Recently ALS/PDC has dramatically decreased in prevalence, confirming its environmental etiology. CTE is a disorder seen following repeated impact traumatic brain injuries, especially among contact sport participants. It is characterized by widespread tau pathology in the form of NFTs, astrocytic tangles and tau threads in a characteristic pattern not shared by other forms of tauopathy. These three disorders provide insights into the environmental side of nature/nurture interactions leading to neurodegeneration although the mechanism/s underlying this phenomenon remains unclear. For non-neurologic diseases, avoiding relevant environmental factors represents an effective means to reduce prevalence. Robust inquiries into environmental factors in neurodegenerative disease could represent an effective means by which the impact of these conditions could also be reduced.
Consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

Nigel J. Cairns¹, Ann C. McKee²,³,⁴,⁵,⁶, Dennis W. Dickson⁷, Rebecca D. Folkerth⁸, C. Dirk Keene⁹, Irene Litvan¹⁰, Daniel P. Perl¹¹, Thor D. Stein³,⁴,⁵,⁶, Jean-Paul Vonsattel¹², William Stewart¹³, Yorghos Tripodis⁴,¹⁴, John F. Craty¹⁵, Kevin F. Bieniek⁷, Kristen Dams-O'Connor¹⁶, Victor E. Alvarez²,³,⁴,⁵, Wayne A. Gordon¹⁶, the TBI/CTE group

¹Department of Neurology, Washington University, Saint Louis, Missouri, USA, ²Department of Neurology, Boston University School of Medicine, Boston, USA, ³Department of Pathology, Boston University School of Medicine, Boston, USA, ⁴Alzheimer's Disease Center, CTE Program, Boston University School of Medicine, Boston, USA, ⁵VA Boston Healthcare System, Boston, USA, ⁶Department of Veteran Affairs Medical Center, Bedford, USA, ⁷Department of Neuroscience, University of California San Diego School of Medicine, La Jolla, USA, ⁸Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA, ⁹Department of Pathology, University of Washington School of Medicine, Seattle, USA, ¹⁰Department of Neurosciences, University of California San Diego School of Medicine, La Jolla, USA, ¹¹Taub Institute for Research on Alzheimer's disease and the Aging Brain, Columbia University Medical Center, New York, USA, ¹²Department of Neuropathology, University of Glasgow Institute of Neuroscience and Psychology and Queen Elizabeth University Hospital, Glasgow, UK, ¹³Department of Biostatistics, Boston University School of Public Health, Boston, USA, ¹⁴Department of Pathology, Fishberg Department of Neuroscience, Friedman Brain Institute, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai School, New York, USA, ¹⁵Department of Pathology, Center for Neuroscience and Regenerative Medicine, Uniformed Services University of the Health Sciences, Bethesda, USA, ¹⁶Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, USA,

Introduction: Chronic traumatic encephalopathy (CTE) is a neurodegeneration characterized by the abnormal accumulation of hyperphosphorylated tau protein within the brain. Like many other neurodegenerative conditions, CTE can only be definitively diagnosed by post-mortem examination of brain tissue. A consensus panel funded by the National Institute of Neurological Disorders and Stroke and the National Institute of Biomedical Imaging and Bioengineering (NINDS/NIBIB) was convened to define the neuropathological criteria for CTE.

Methods: Twenty-five cases of various tauopathies were selected. The cases included 10 cases of suspected CTE and other cases that may have overlapped or be confused with CTE included Alzheimer disease (n=5), progressive supranuclear palsy (n=2), corticobasal degeneration (n=2), parkinsonism/dementia complex of Guam (n=2), argyrophilic grain disease (n=2), and primary age-related tauopathy (n=2). From 27 representative areas, sections were stained with Luxol fast blue counterstained with hematoxylin and eosin and a Bielschowsky silver impregnation; immunohistochemistry was performed using anti-Aβ42, anti-phosho-tau and anti-phospho-TDP-43. The 671 glass slides were scanned into digital images using an Aperio scanner (Leica Biosystems, Buffalo Grove, IL. No clinical or demographic information was provided to the evaluating neuropathologists.

Results: There was good agreement regarding the overall neuropathological diagnosis of all 25 cases (Cohen's kappa, 0.67), and even better agreement regarding the specific diagnosis of CTE (Cohen's kappa, 0.78), using the proposed criteria. Three initial diagnoses of non-CTE were changed to CTE and nine diagnoses of co-morbid CTE in non-CTE cases were changed to no CTE after revealing the clinical and gross neuropathological features.

Conclusion: A consensus panel of seven neuropathologists concluded that the pathology of CTE is distinct from other tauopathies. The panel described the pathognomonic lesion of CTE as an accumulation of abnormal tau in neurons and astroglia distributed perivascularly at the depths of sulci in the isocortex in an irregular pattern.
Chronic traumatic encephalopathy (CTE), a brain disorder characterized by the intracytoplasmic accumulation of misfolded tau in neurons and glia, has been recognized to be caused by the repetitive head traumas associated with the practice of several types of contact sports. In the 1920-30's, descriptions of the “punch drunk” neurological syndrome of professional pugilists were reported, and the first neuropathologic descriptions of boxers' brains were published 30-40 years later. The macroscopic and microscopic findings consisted of abnormalities of the septum pellucidum, cerebellar scarring, neurofibrillary degeneration, particularly severe in the temporal lobes, and degeneration of neurons of the substantia nigra and locus coeruleus. As early as the 1880's, concussions among college football players were already of concern; however, it was not until the mid 2000's that autopsies of former professional football players revealed the neuropathologic features of CTE, linking tau pathology to repetitive head injuries in footballers. CTE has recently been described in association with other sports, including soccer, rugby, mixed martial arts, and hockey. In 2016, neuropathologic criteria for CTE were established. In contrast to other tau pathologies, the spatial distribution of perivascular tau aggregates in neurons and glia, notably at the depth of sulci, is considered pathognomonic. Impact-injuries and distribution of brain changes may differ among athletes due to differences in the mechanisms of and/or risks for head injuries relevant to each sport. Individual genetic risks for the development of CTE may also contribute. At present, a definitive diagnosis of CTE is made only through postmortem neuropathology. However, Tau-PET neuroimaging and other biomarkers may lead to CTE diagnosis during life, possibly during early, even clinically silent, stages of disease. Biomarkers of early stages of neurodegeneration may be useful to recognize clinical stages of CTE and help identify individuals at risk for CTE for early treatment when novel therapies become available.
Neuropathology of Familial Amyotrophic Lateral Sclerosis and Parkinsonism dementia Complex from the Hohara focus of the Kii Peninsula: a tau-dominant multiple proteinopathy

Maya Mimuro¹, Mari Yoshida¹, Shigeki Kuzuhara², Yasumasa Kokubo³

¹ Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University,  
² Faculty of Nursing, Suzuka University of Medical Science,  
³ Kii ALS/PDC Research Center, Mie University Graduate School of Regional Innovation Studies

The Kii peninsula of Japan is one of the high incidence foci of amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia complex (PDC) in the Western Pacific. Recently, Kii ALS/PDC is considered as a heterogeneous syndrome of several different causes including both genetic and environmental factors. In this symposium, we present the neuropathology of familial cases of ALS/PDC from Hohara, the eastern focus of Kii ALS/PDC, which is characterized tau-dominant multiple proteinopathy. Eighteen cases were submitted for this study. Clinically, they showed motor neuron signs and/or parkinsonism with dementia. Pathologically, their brains showed accumulation of various proteins, including tau, TDP-43, and alfa-synuclein (αSyn). NFTs were predominantly found in the superficial layers of the cerebral cortex and ghost tangles were abundant. Neuropil threads were scarce compared with Alzheimer's brains. Tau-positive astrocytes were observed mainly at subpial and perivascular regions. Tau deposition in both neurons and astrocytes were the common neuropathological features of all cases. pTDP-43-positive neuronal cytoplasmic inclusions were observed in all brains, mainly in the limbic system. Bunina bodies and skein-like inclusions were observed in 65%, and Lewy body pathology, in 77% of them. Among them, cases with pTDP-43-predominant deposition clinically showed signs of ALS, while cases with αSyn-predominant deposition showed signs of PDC. From the above findings, we have concluded that ALS/PDC from Hohara is a single familial disease characterized by tau-dominant multiple proteinopathy though clinical manifestations differed among the cases.
Axonal Pathology in Multiple Sclerosis

Hans Lassmann

Center for Brain Research, Medical University of Vienna

Multiple sclerosis is a chronic inflammatory disease of the central nervous system leading to focal plaques of demyelination and diffuse neurodegeneration in the brain and spinal cord. Although demyelination is the hallmark of MS pathology, axons degenerate within the lesions and diffusely in the normal appearing white and grey matter. Axonal loss is a major structural correlate of permanent functional deficit in the patients. In focal white matter lesion the bulk of axonal injury occurs during the stage of active demyelination. In addition, however, there is a slowly progressive axonal injury in chronic demyelinated plaques, which is massively reduced or even absent, when the lesions are remyelinated. Axonal and neuronal degeneration in the lesions of the white and grey matter results in secondary Wallerian degeneration in the normal appearing white and grey matter, thus providing a major contribution to global axonal loss and atrophy in the brain and spinal cord. In addition, acute axonal injury and neuronal degeneration also takes place independent of focal demyelinated lesions, being associated with inflammation in the meninges, in the large perivascular spaces and in the central nervous system parenchyma. A variety of different mechanisms have been suggested to drive axonal and neuronal degeneration in MS, including T-cell mediated cytotoxicity, autoantibodies and activation of innate immune mechanisms. A prominent pathogenic cascade of neurodegeneration in MS involves oxidative stress, resulting in mitochondrial damage and subsequent energy failure. Neurodegeneration through this mechanism is amplified by the increased energy demand of demyelinated axons.
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which leads to focal destruction of myelin, acute axonal damage/loss of axons and reactive astrogliosis in the white and grey matter. Myelin and oligodendrocytes are the main target of the inflammatory response, however the extent of remyelination as well as the loss or survival of mature oligodendrocytes and oligodendrocyte precursor cells varies between different disease stages as well as between white and grey matter. The present lecture focusses on the extent of remyelination in white and grey matter lesions in early and progressive disease stages. In addition, the pathology of mature oligodendrocytes as well as oligodendrocyte precursor cells is discussed. In general, remyelination is more extensive in grey than in white matter. Whereas mature oligodendrocytes are extensively present in early disease stages, they completely disappear in progressive MS. Oligodendrocyte precursor cells in contrast are still detectable in chronic lesions, however they fail to differentiate into myelinating cells. Preservation of oligodendrocytes is better in grey than white matter lesions and there is a clear age-dependent decrease in the numbers of oligodendrocyte precursor cells. In summary, the major pathological differences between relapsing-remitting and progressive multiple sclerosis related to oligodendrocyte pathology and remyelination are discussed.
Environmental control of astrocyte pathogenic activities in CNS inflammation

Francisco J. Quintana\textsuperscript{1,2}

\textsuperscript{1} Center for Neurologic Diseases, Harvard Medical School, \textsuperscript{2} The Broad Institute of Harvard and MIT

Astrocytes play important roles in the central nervous system (CNS) during health and disease. Thus, the identification of factors that regulate astrocyte activity may shed light on CNS physiology and guide new therapies for human neurologic disorders. In this class we will discuss mechanisms used by astrocytes to control CNS inflammation. In addition, we will discuss molecular pathways involved in the control of astrocyte function. For example, we recently found that microbial metabolites limit astrocyte pathogenic activities in the context of CNS inflammation. Specifically, metabolites of dietary tryptophan activate aryl hydrocarbon receptor (AHR) signaling in astrocytes to limit CNS inflammation and neurodegeneration. In addition, these metabolites also activate AHR on microglia to limit their intrinsic pathogenic activities and to modulate their ability to modulate astrocytic responses via the secretion of TGF-alpha and VEGF-B. Microglia-derived TGF-alpha acts via ErbB1 in astrocytes to limit their pathogenic activities and EAE development. Conversely, microglial VEGF-B triggers FLT-1 signaling in astrocytes and worsens EAE. VEGF-B and TGF-alpha also participate in the microglial control of human astrocytes. In summary, we identified novel positive and negative regulators that mediate the microglial control of astrocytes. Moreover, these findings define a novel gut/brain pathway through which microbial metabolites limit pathogenic activities in microglia and astrocytes, suppressing CNS inflammation. This pathway may guide new therapies for MS and other neurologic disorders.
This year marked the 150th anniversary of clinical description with pathological evidence of multiple sclerosis (MS) by Leopold Ordenstein (1835-1902) and his mentor, Jean-Martin Charcot (1825-1893) in Paris (1868). They investigated the most comprehensive study on MS and Parkinson disease (PD) at that time, and represented a clear hallmark of MS in comparison with PD. Now, 150 years later, we have an increased knowledge of pathogenesis in MS and its related diseases. In particular, the discovery of aquaporin-4 (AQP4) antibodies as a diagnostic biomarker of neuromyelitis optica (NMO) in 2005 is a landmark in the research history of MS and its related diseases. NMO is defined as 'AQP4-opathy', because AQP4 autoantibodies and activated complements should target AQP4 water channels on astrocytes or ependymal cells in the CNS. On the other hands, MS is a disease primarily affecting myelin and oligodendrocytes, but the details of autoantigens have remained unclear. MS and NMO have distinct immunological and pathological features with different degrees of severity and pathogenetic mechanisms. The distinct inflammatory processes in these diseases may trigger cascades of events leading to disease-specific or nonspecific neurodegeneration, via dysfunction or activation of astrocytes, oxidative burst activation in microglia/macrophages, mitochondrial damage and axonal energy failure, Wallerian degeneration and meningeal inflammation. The comparative consideration of 'inflammation and neurodegeneration' between MS and NMO will again highlight the most important issue, 'what are the hallmarks of MS?'. 
Prion and Prion disease: An overview and challenges

Hidehiro Mizusawa¹,²

¹National Center of Neurology and Psychiatry, ²Tokyo Medical and Dental University

Prion diseases are devastating neurodegenerative diseases in humans such as Creutzfeldt-Jakob disease (CJD) and many animal species including sheep, cow, deer and cat. CJD presents rapidly progressive dementia and other symptoms resulting in 100 percent death usually in months without any medicine to treat. Most CJD cases are sporadic and of unknown origin. There are also genetic forms such as genetic CJD, Gerstmann-Sträussler-Scheinker syndrome and Fatal Familial Insomnia and, rarely, acquired forms including iatrogenic CJD such as due to human dura mater grafts or human pituitary derived hormones.

Prion diseases are caused by conversion of normal prion proteins to transmissible (infective) abnormal prion proteins (prion). Three Nobel Prizes have been awarded in this narrow field of science but mechanisms of conversion, transmission and neuronal degeneration are far from elucidation.

Fortunately the outbreak of variant CJD transmitted through foods contaminated with prion of bovine spongiform encephalopathy was almost eliminated but unfortunately mechanism of infection to young adults is unknown. Chronic wasting disease of deer spreading in north America, south Korea and recently in northern Europe appears an emerging threat to us.

Recent studies on A-beta, Tau, alpha-synuclein and others linked to Alzheimer's disease, Parkinson's disease and so on demonstrated they also share characteristics with prion proteins, notably auto-aggregation, self-propagation and induction of lesions in animals. These findings suggest that research and development of treatment on Prion disease would contribute greatly to overcome such neurodegenerative diseases. International cooperation all over the world is crucial in overcoming Prion diseases.
Neuropathology of prion diseases: principles and more

Gabor G. Kovacs

Institute of Neurology, Medical University of Vienna, Vienna, Austria

Prion diseases may be triggered through infection, germline mutations in PRNP, and most frequently by yet unidentified “sporadic” events that generate disease-associated PrP. Classical light microscopic features of prion diseases include spongiform change, neuronal loss, and astro- and microgliosis. Amyloid plaques are seen only in a subset of prion diseases. Immunostaining for disease-associated PrP reveals a wide range of morphologies from fine to coarse and plaque-like deposits. The codon 129 polymorphism in combination with the Western blot pattern of PrPres serves as a basis for molecular subtyping of sporadic Creutzfeldt-Jakob disease (CJD) and is important to distinguish the BSE-related variant CJD characterized by florid plaques in neuropathology. Genetic prion diseases are associated either with parenchymal or vascular PrP amyloidosis, with CJD–like features, or with thalamic degeneration as in fatal familial insomnia. Furthermore, novel phenotypes, including the variably protease sensitive prionopathy or the PrP systemic amyloidosis, or yet unclassifiable forms such as the dementia with thalamic degeneration and peculiar cortical PrP immunoreactivity, have been also described. Studies on the intracellular processing and regional distribution patterns of disease-associated PrP, or the description of concomitant proteinopathies in prion diseases contributed to the understanding of other neurodegenerative diseases. Interestingly, amyloid-beta is mostly associated with iatrogenic CJD, tau pathology is more frequently seen in sporadic CJD and variant CJD, while genetic prion diseases show distinct combinations of additional proteinopathies including amyloid-beta, tau, and alpha-synuclein, but not TDP-43. Thus, neuropathology still provides remarkable observations to unravel the secrets of prion diseases and those with prion-like features.
What is abnormal prion protein (PrPSc)?

Atsushi Kobayashi

Laboratory of Comparative Pathology, Graduate School of Veterinary Medicine, Hokkaido University

A conformational conversion of normal cellular isoform of prion protein (PrP^C) into abnormal misfolded isoform (PrP^Sc) is the central event in the pathogenesis of prion diseases. Although the structure of PrP^C is well defined, the structure of PrP^Sc has resisted high-resolution determination due to its insolubility and propensity to aggregation. Here, I summarize the current knowledge about the structure of PrP^Sc to shed light on the molecular mechanisms for the conformational conversion, neurotoxicity, and prion strain phenomena.
Neuropathology of V180I genetic CJD

Yasushi Iwasaki
Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University

Creutzfeldt-Jakob disease (CJD) with causative point mutation of valine to isoleucine at codon 180 of prion protein (PrP) gene (V180I gCJD) is the most frequent form of gCJD in Japan, whereas this variant is extremely rare in Europe and North America. Previous reports on V180I gCJD have indicated the presence of extensive spongiform changes in the cerebral cortex and striatum and the absence of apparent cerebellar and brainstem lesions despite prolonged disease duration. Diffuse vacuoles in the cerebral cortex are observable macroscopically by loupe on the images of HE-stained tissue. Gliosis, hypertrophic astrocytosis, and neuron loss are generally mild compared to those in sporadic CJD (sCJD) cases with prolonged disease duration in the cerebral cortex, despite the presence of innumerable vacuoles. The morphology of the vacuoles showed various-sized and non-confluent (VaSNoC) type. VaSNoC-type vacuoles are visually different from the fine vacuoles observed in MM1-type sCJD, as well as from the large confluent vacuoles observed in MM2-cortical type sCJD. The appearance of VaSNoC-type vacuoles in the cerebral cortex is considered a feature of V180I gCJD. The characteristic vacuoles show no expansion with disease progression. In addition, the dispersion of the major vacuole diameters is larger than that in the MM1-type, and smaller than that in the MM2C-type. The presence of VaSNoC-type vacuoles in the cerebral neocortex of patients with CJD is useful for predicting V180I mutation prior to PrP gene analysis. With regard to prion protein immunostaining, very weak synaptic-type deposition is recognized.
Neuropathology of FAP type prion disease

Kota Sato, Jingwei Shang, Mami Takemoto, Nozomi Hishikawa, Yasuyuki Ota, Koji Abe

Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Introduction: In most prion diseases, cognitive functions are commonly affected. However, a novel type of prion disease has recently been reported that is associated mainly with autonomic-sensory polyneuropathy. We experienced two siblings (patient 1 and 2) who showed chronic progressive autonomic-sensory polyneuropathy with novel PRNP gene mutation of c.534_535delCT(p.Asp178fs).

Results: Patient 1 showed urinary retention at age 26, then began to present orthostatic hypotension at age 30. After the age of 31, she suffered from frequent vomiting and diarrhea. At age 34, her limbs presented thermoanesthesia and hypoalgesia, and her tendon reflexes showed generalized areflexia. Compound muscle action potentials and sensory action potentials were not evoked in bilateral tibial and sural nerves, respectively. Sural nerve biopsy revealed moderate loss of myelinated fibers with not amyloid material, but anti-3F4 staining revealed ragged deposits. Cerebrospinal fluid levels of 14-3-3 and tau proteins were elevated. She suffered severe pneumonia and died at age 37. Her cerebral cortices showed severe spongiosis and neuropil degeneration. Anti-3F4 staining showed coarse deposits in the cerebral cortex, the small vessels, and deposits in almost all other organs. Patient 2 began to suffer from frequent diarrhea at age 20, orthostatic hypotension at age 28, urinary retention at age 30, vomiting at age 32 and thermoanaesthesia at age 34. Similar to patient 1, anti-3F4 staining in patient 2 revealed remarkable deposits of PrP in his sural nerve.

Conclusions: The present familial cases provide a very important suggestion for elucidating an exact mechanism of this particular prion disease.
Rare brain tumor diagnosis: reassessment in the era of methylation profiling

David Capper\textsuperscript{1,2}

\textsuperscript{1}Institute of Neuropathology, Charité-Universitätsmedizin Berlin,
\textsuperscript{2}German Cancer Consortium (DKTK), Partner Site Berlin / German Cancer Research Center (DKFZ), Heidelberg, Germany

Genome-wide DNA methylation profiling is evolving as a promising tool for brain tumor classification and the identification of new biological tumor classes. In this presentation, the possibilities to refine the diagnosis of several rare brain tumors such as anaplastic pilocytic astrocytoma, diffuse leptomeningeal glioneuronal tumor, olfactory neuroblastoma, astroblastoma and isomorphic astrocytoma will be presented. Further, more general technical aspects of DNA methylation profiling will be discussed as well as possible future developments in the field of rare brain tumors.
Exosomal miRNAs as blood-based biomarkers in glioblastoma

Michael E Buckland\textsuperscript{1,2}

\textsuperscript{1} Department of Neuropathology, Royal Prince Alfred Hospital,  
\textsuperscript{2} Brain & Mind Centre, University of Sydney, Sydney, Australia

[Introduction] There is growing interest in 'liquid biopsies' in cancer diagnosis and management. Commonly used assays include cell free DNA and 'free circulating' RNA such as microRNA (miRNA). Exosomes are nano-sized extracellular vesicles released by many cells that contain a distinct molecular cargo, including miRNA and DNA. Exosomes released by glioblastoma cross the blood-brain-barrier and can be detected in the peripheral circulation.  

[Methods] Serum exosomal-miRNAs were isolated from glioblastoma (n=12) patients and analysed using unbiased deep sequencing. Results were compared to sera from age- and gender-matched healthy controls, and to grades II-III (n=10) IDH-mutant glioma patients. Additional sera from glioblastoma patients (n=4) and independent sets of healthy (n=9) and non-glioma (n=10) controls were used to further test the specificity and predictive power of this exosomal-miRNA signature.  

[Results] Twenty-six miRNAs were differentially expressed in serum exosomes from glioblastoma patients relative to healthy controls. Random forest modelling and data partitioning selected seven miRNAs as the most stable for classifying glioblastoma. Within this model, two iterations of these miRNA classifiers could distinguish glioblastoma patients from controls with perfect accuracy. The seven miRNA panel was able to correctly classify all specimens in validation cohorts (n=23). Also identified were 23 dysregulated miRNAs in to grades II-III (n=10) glioma patients; a partially overlapping yet distinct signature of lower grade glioma.  

[Conclusions] This preliminary study demonstrates a strong signal of glioblastoma in peripheral blood exosomal miRNA. Longitudinal studies of larger patient populations are underway to determine the clinical utility of these assays.
Brain region specific molecular profile of cerebellar gliomas

Masashi Nomura¹², Akitake Mukasa³, Shota Tanaka¹, Yoshitaka Narita⁴, Motoo Nagane⁵, Keisuke Ueki⁶, Ryo Nishikawa⁷, Junji Shibahara⁸, Hiroyuki Aburatani², Nobuhito Saito¹

¹ Department of Neurosurgery, Graduate School of Medicine, The University of Tokyo, ¹² Genome Science Division, Research Center for Advanced Science and Technology, The University of Tokyo, ³ Department of Neurosurgery, Graduate School of Medical Sciences, Kumamoto University, ⁴ Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, ⁵ Department of Neurosurgery, Kyorin University Faculty of Medicine, ⁶ Department of Neurosurgery, Dokkyo Medical University, ⁷ Department of Neuro-Oncology/Neurosurgery, Saitama International Medical Center, Saitama Medical University, ⁸ Department of Pathology, Kyorin University Faculty of Medicine

Recent profiling efforts of gliomas have demonstrated different alterations among patient's age groups and originated brain regions. For example, H3K27M mutation, which disrupts epigenetic regulation globally and leads to tumorigenesis, occurs frequently in pediatric midline gliomas. These specific profiles have been suspected to be associated with glial and neuronal development. In this study, we analyzed cerebellar gliomas, which have not been studied enough, using whole-exome sequencing (17 cases), RNA-sequencing (14 cases), and methylation array (17 cases). The genomic analysis revealed frequent mutations in chromatin-regulation genes and p53-related genes. On the other hand, mutations and copy number changes commonly observed in cerebral gliomas were infrequent. Methylation and expression analyses combined with data of 315 gliomas originated from each anatomical region identified different regulation of transcription factor genes including SOX10, OLIG1/2 and FOXG1, which play an important role in normal developmental programs of central nervous system, reflecting distinct cellular-origin of gliomas at each anatomical region. The pattern of cerebellar gliomas was close to that of oligodendrocyte precursor cell lineage. These findings suggested regional specificity of gliomas and may provide potential of tailored targeted therapy for gliomas according to the cellular-origin.
Identification of the therapeutic targets for brain tumor-related fusion genes using an animal model

Tatsuya Ozawa¹, Syuzo Kaneko², Mutsumi Takadera¹, Zhiwei Qiao³, Frank Szulzewsky⁴, Tadashi Kondo³, Eric C. Holland⁴, Ryuji Hamamoto², Koichi Ichimura¹

¹ Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Japan,
² Division of Molecular Modification and Cancer Biology, National Cancer Center Research Institute, Japan,
³ Division of Rare Cancer Research, National Cancer Center Research Institute, Japan,
⁴ Division of Human Biology, Fred Hutchinson Cancer Research Center, Washington, USA

Fusion genes provide therapeutic insight as the breakpoints highlight cancer-relevant genes. In contrast to druggable kinase fusions, it is not easy to identify the therapeutic targets for ones composed of an unpredictable domain such as a transcription factor, thus likely necessary to examine the molecular function in detail. The genetically engineered mouse model is an essential tool for current cancer research but has the critical drawback which cannot perfectly reproduce the complex molecular heterogeneity of human cancers because a limited number of genes is enough to induce tumors in mice. However, given the potential driver function of the fusions, the model appears to fit for their functional analysis. So far, we have presented that the C11orf95-RELA fusion, recently identified in ependymomas (EPNs) was a potent oncogene capable of inducing human EPN-like tumors in an RCAS/tv-a retroviral gene transfer system. In this talk, we would demonstrate to explore for the therapeutic targets of the C11orf95-RELA fusion through the functional analyses and drug screening with our EPN model, and then the application of our experimental approach to other brain tumor-related fusions to identify the therapeutic targets.
Clinical results of patients with lower grade gliomas in our institute and surgical strategy using intraoperative molecular diagnosis

Masayuki Nitta\textsuperscript{1,2}, Yoshihiro Muragaki\textsuperscript{1,2}, Takashi Maruyama\textsuperscript{1,2}, Taiichi Saito\textsuperscript{1}, Shunsuke Tsuzuki\textsuperscript{1}, Shunichi Koriyama\textsuperscript{1}, Takashi Komori\textsuperscript{3}, Takakazu Kawamata\textsuperscript{1}

\textsuperscript{1}Department of Neurosurgery, Tokyo Women's Medical University, \hspace{1cm} \textsuperscript{2}Faculty of Advanced Techno-Surgery (FATS), Institute of Advanced Biomedical Engineering & Science, Graduate School of Medicine, Tokyo Women's Medical University, \hspace{1cm} \textsuperscript{3}Department of Pathology, Tokyo Metropolitan Neurological Hospital

\textbf{Introduction} In the 2016 WHO classification, genetic information was introduced in the pathology diagnosis of gliomas, and the correlation between genotype and prognosis has been shown. Correlation between extent of removal (EOR) and prognosis has been shown, but it is often difficult to achieve both high EOR and preservation of brain function. Here, we report the clinical results of lower grade gliomas (LGGs) in the WHO new classification at our facility and discuss the significance of the surgical strategy based on intraoperative rapid molecular diagnosis that our institution is working on.  

\textbf{Methods} In 366 cases (G2 219 cases, G3 147 cases) with newly diagnosed LGGs that could be classified according to 2016 WHO classification in our hospital (2004-2014), the relation between the EOR and prognosis was retrospectively analyzed. Accuracy of intraoperative rapid molecular diagnosis of IDH mutation and 1p/19q codeletion using HRM method and p53 / ATRX immunostaining was evaluated.  

\textbf{Result} The 10-year survival rate of oligodendroglioma was 88% in G2 (121 cases), 80% in G3 (59 cases), the 10-year survival rate of DA-IDH mutant was 63% in G2 (66 cases), MST of G3 (46 cases) was 13.6 years, MST of DA - IDH wild-type was G2 (32 cases) 12.6 years, G3 (42 cases) 3.9 years. The EOR correlated with prognosis in DA-IDH wild-type G2.  

\textbf{Conclusion} In the LGGs, the prognosis and the significance of EOR was significantly different between subtypes. Rapid intraoperative molecular diagnosis seems to be useful for determining the removal strategy in lower grade glioma surgery.
Genome-wide DNA methylation profiling reveals molecular heterogeneity of anaplastic pleomorphic xanthoastrocytoma

Taishi Nakamura¹, Koishi Ichimura²

¹Department of Neurosurgery, Graduate School of Medicine, Yokohama City University, Yokohama, Japan,
²Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan

Anaplastic pleomorphic xanthoastrocytoma (PXA) has been newly defined as a variant of the PXA entity in the revised WHO classification 2016. Furthermore, some anaplastic PXAs were reported extremely poor prognosis, which showed a similar molecular profiles to pediatric glioblastomas (GBMs). Recent integrated molecular classification for primary CNS tumors proposed some discrepant separations between histological feature and that of molecular. Herein we present an extreme aggressive anaplastic PXA which housed pediatric GBM molecular profile in genome-wide molecular analysis. A full implementation of molecular approach is the key to predict prognosis and determine treatment strategy for anaplastic PXAs.
The diversity of pediatric high grade gliomas

Akihide Kondo¹, Atsushi Arakawa², Mario Suzuki¹, Osamu Akiyama¹, Hajime Arai¹

¹ Department of Neurosurgery, Juntendo University, Tokyo, Japan,
² Department of Human Body Pathology, Juntendo University, Tokyo, Japan

[Background]
The high-grade glioma in children is biologically diverse in the form of molecular biology. Even in the classification in 2016, it is difficult to say we have a comprehensive idea about these tumors. Since a new entity appeared in it. In recent reports, depending on the onset age, the molecular biological factor is different even if the morphology is similar. It has been also reported that the treatment prognosis is various depending on their molecular characters.

[Patients]
We encountered the kids suffering from high-grade gliomas who had a surgery in our institution. We examined tumor specimens obtained from the surgeries.

[Results]
Clinical course and specimen analysis of six cases were possible. The ages were from 0 to 13 years old, and all were diagnosed as high-grade glioma in morphologically. In five cases, we carried out molecular biological analysis.

[Conclusion]
The prognosis and the tumor characteristics were examined by age. By comparing the facts those had been reported with our pathological image and the molecular biological factors, specific trend could be seen in our series.
Clinicopathological features of pediatric supratentorial high grade glioma

Koji Yoshimoto¹, Hiroyuki Uchida¹, Hajime Yonezawa¹, Nobuhiro Hata², Masahiro Mizoguchi², Hirofumi Hirano¹

¹Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Japan, ²Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

【Objective】Pediatric supratentorial high grade glioma includes various histological type of tumors. Since the introduction of new diagnostic criteria Diffuse midline glioma, H3 K27M-mutant in WHO2016 classification, we need to integrate the pathological diagnosis and molecular diagnosis. In this study, we aim to retrospectively analyze the clinicopathological features of pediatric supratentorial high grade glioma. 【Materials and methods】We collected 20 pediatric supratentorial high grade glioma cases which were operated as initial surgery during the period after 2000 in the two institutions to which first author belong. Patient age ranged from 3 to 20 years old (median 11y). Main tumor locations were as follows: thalamus/basal ganglia, 10cases; frontal lobe and parietal lobe, 4cases, respectively; temporal lobe, 2cases. DNA-based or immunohistochemical analysis to detect H3F3A mutations were performed in 12 cases out of total 20 cases. 【Results】Histopathological diagnosis based on WHO 2007 criteria was glioblastoma 13 cases, astroblastoma 3 cases, anaplastic ependymoma 2 cases, anaplastic astrocytoma 1 case, PNET 1 case. K27M mutations were detected in 6/10 glioblastoma, and one case of anaplastic ependymoma, whereas two cases of glioblastoma and a astroblastoma were G34R mutation. Accordingly, 7 cases out of 12 cases can be diagnosed as Diffuse midline glioma, H3 K27M-mutant. 【Conclusions】Diffuse midline glioma, H3 K27M-mutant occurs in the midline region, and include not only astrocytic high grade tumors but also other morphological tumors.
Post mortem radiological imaging, most widely available in the form of post mortem CT scanning, if used appropriately, can optimise and value add to the forensic neuropathological examination by assisting in case triage, targeting areas of interest, demonstrating features not readily seen on routine examination, documenting extensive neurosurgical intervention, and providing a complimentary data set, which when added to conventional neuropathological findings, can provide useful case data to forensic investigators. These scenarios will be discussed, along with the utility of post mortem CT angiography.
Vascular complications of traumatic head injury

Daniel du Plessis\textsuperscript{1,2}

\textsuperscript{1} Greater Manchester Neurosciences Centre, Salford Royal Hospital,  
\textsuperscript{2} Dept of Paediatric Pathology, Alder Hey Children's Hospital

Secondary vascular compromise is a common complication of post-traumatic brain swelling, comprising global hypoxic-ischaemic brain injury, bleeds and herniation-related infarction. Primary cranio-cervical arterial and/or venous injuries are less commonly encountered. Such pathologies are though under-recognised, a status contributed to by limited reporting in the literature, compounded by poor documentation and suboptimal investigative approaches in the past. Despite the relatively rare occurrence of such pathologies, a pro-active, anticipatory approach to such injuries should be promoted in forensic practice. It is further necessary to emphasize that some such vascular injuries may only require minor trauma and on occasion occur spontaneously, mimicking traumatic head injury including non-accidental injury. A high index of suspicion is essential to avoid diagnostic neglect or error. Traumatic basal subarachnoid haemorrhage serves as a model in this regard, the diagnosis and recognition of which has benefited from more rigorous, focused dissection and sampling protocols. Pathophysiological issues around cause and effect though remain to be elucidated fully. The spectrum of traumatic arterial vascular traumatic injury further includes cranio-cervical arterial dissection and traumatic intracranial aneurysms. Some such injuries have been described in a setting of relatively minor trauma, again focusing attention on susceptibility factors including underlying, predisposing connective tissue disorders. Cerebral venous thrombosis is another under-recognised complication of traumatic head injury in all age groups. CVT attracted some controversy following a suggestion that complications may mimic paediatric non-accidental head injury.
Inflicted traumatic brain injury in infants: An update on neuropathology and ophthalmopathology with a reassessment of the role of the brainstem

Jakob Matschke¹²

¹ Forensic Neuropathology Unit, ² Institute for Neuropathology, University Medical Centre Hamburg-Eppendorf

Inflicted traumatic brain injury in infants comprises mostly the so-called shaken baby syndrome and a few other rarer conditions. Neuropathologists are often asked to give oral or written expertise for investigative authorities. Yet an expertise in a manner that will stand up in court requires a broad knowledge of the pathomorphology and a sound understanding of the underlying pathomechanisms. This talk will summarize the current knowledge of inflicted traumatic brain injury in infants and give an critical overview of its facts, myths and controversies. A special consideration is given to the role of local traumatic injury to the brainstem and the pathophysiological consequences hereof.
Brain Swelling: Issues of Recognition, Aetiology and Timing – Insights from the Hillsborough Stadium disaster in the United Kingdom

Daniel du Plessis
Greater Manchester Neurosciences Centre and Alder Hey Children's Hospital, Liverpool

The 1989 Hillsborough Stadium disaster was the worst British sporting disaster. The original inquests controversially determined that all deaths occurred shortly after a sudden influx of spectators. A 2012 review concluded that several of the 96 fatalities might have survived, an opinion in part informed by the original post-mortem examination findings, which suggested that many victims had brain swelling and were thus subject to more prolonged survival. Review of the postmortem findings to assist the 2014 reinquests expressed concern about the accuracy of such descriptions, although brain weights were disproportionately high. It was also concerned by the incorrect assumption that brain swelling necessarily reflected cerebral oedema. Consideration was given to alternative (and far more rapid) mechanisms of brain swelling such as perfusion swelling due to loss of autoregulation or passive congestion due to venous outflow obstruction. Comparison with other modes of asphyxial death including hangings or static forms of crush asphyxia provided some possible further insight. Crush asphyxia in a crowd situation may be subject to more complex pathophysiology given a waxing and waning effect rather than static compression.

Review of the neuropathology of the 96 deaths highlighted pitfalls in the assessment of brain swelling at postmortem and emphasized the need for an integrated approach relying on a combination of features to enhance objectivity and reliability. It also emphasizes the necessity not to assume that all swelling is oedema as the latter may have profound medico-legal implications in terms of potential survival.
SUDEP as a cause of sudden death

Maria Thom

Department of Neuropathology, Institute of Neurology, University College London

Sudden unexpected death in epilepsy (SUDEP) primarily affects young adults with epilepsy. The incidence is estimated as 1 to 2 cases per 1000 people with epilepsy per year from population based studies. SUDEP is geographically widespread, can affect all age groups and epilepsies with diverse underlying causes with frequent generalised seizures being the greatest risk factor. The years of potential life lost from SUDEP is second only to stroke for neurological conditions and the International League Against Epilepsy (ILAE) now recognises SUDEP as a global healthcare concern which has been previously underestimated. SUDEP is defined as an unexpected and non-accidental death in patient with epilepsy (excluding status epilepticus), where no cause of death is identified following complete post-mortem examination. Deaths occur around the time of a seizure, although many are unwitnessed. Although the mechanisms and pathophysiology are still uncertain, accumulating evidence from clinical, imaging (structural and functional imaging) and experimental studies indicates that central autonomic regulatory control of vital cardio-respiratory functions is involved.

It is vital that a uniform and standardized autopsy and neuropathological examinations are conducted in these cases for correct cause of death categorization of SUDEP and its distinction from other epilepsy related deaths. Furthermore, systematic post mortem tissue banking in conjunction with parallel molecular genetic analysis will be vital to further future research programs. For example, recent neuropathology studies have highlighted alterations to neuromodulatory neuronal networks in the medullary respiratory nuclei and central autonomic networks including the amygdala in SUDEP. One hypothesis therefore is that epilepsy and seizures induce aberrant modulation and plasticity in brainstem and central autonomic networks that render the brain more likely to dysfunction during seizure.

This talk aims to overview the current understanding of the neuropathology findings in SUDEP and how tissue based studies could advance our understanding of disease mechanisms.
Neuropathology of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) presenting as either PSP syndrome (PSPS) or corticobasal syndrome (CBS)

Dennis W. Dickson, Shunsuke Koga

Department of Neuroscience, Mayo Clinic

Introduction: PSP and CBD are 4R-tauopathies with overlapping clinical and pathologic features that lead to diagnostic difficulties. Methods: The Mayo Clinic brain bank has 1271 patients with PSPS and 236 with CBS. We reviewed neuropathology to provide insights on diagnostic accuracy. Results: Of patients with PSPS, 1031 had PSP (81% diagnostic accuracy). Other disorders were CBD (6%), Lewy body disease (LBD, 4%), multiple system atrophy (3%), Alzheimer disease (AD, 2%) and cerebrovascular disease (vascular PSP, 1%). For patients with CBS, 61 had CBD (26%). Other disorders were PSP (33%), AD (21%), LBD (6%), frontotemporal lobar degeneration (5%), primary lateral sclerosis (3%) and Pick disease (2%). PSPS with PSP were older at death than those with CBD (74 vs. 69 years). PSPS with PSP had more Alzheimer pathology that PSPS with CBD (median Braak: III vs. I; median Thal: 1 vs. 0). There were no demographic differences in patients with CBS and either PSP or CBD. Almost half of PSP with CBS were atypical PSP, with corticospinal tract degeneration in 48%. In contrast, 5% of CBD with PSPS had atypical pathology and greater hindbrain tau pathology. Argyrophilic grain disease was more frequent in CBD (49%) than PSP (24%), but it had no clear relationship to clinical presentation. TDP-43 pathology was greater in CBD (47%) than PSP (4%). In CBD it was associated with PSPS (60% vs. 30%). Conclusions: Specific pathologic features distinguish PSPS with underlying PSP versus CBD that may lead to biomarkers to improve diagnostic accuracy.
Neuropathology of Parkinson's disease as multicentric Lewy body disorder

Koichi Wakabayashi

Department of Neuropathology, Hirosaki University Graduate School of Medicine

The histological hallmark of Parkinson's disease (PD) and dementia with Lewy bodies (DLB) is neuronal alpha-synuclein aggregates called Lewy bodies and Lewy neurites. To date, more than 100 molecules have been identified in Lewy bodies, in which phosphorylated alpha-synuclein is a major constituent. PD is traditionally considered a movement disorder with lesions in the brainstem pigmented nuclei. However, accumulating evidence suggests that non-motor complications are also common in PD. Braak et al. proposed a pathological staging scheme for PD, in which early alpha-synuclein pathology is present in the dorsal vagal nucleus and in the olfactory bulb. This staging system characterizes a progression from the dorsal vagal nucleus (stage 1), through the pontine tegmentum (stage 2), into the midbrain and neostriatum (stage 3), and then the basal procencephalon and mesocortex (stage 4), and finally through the neocortex (stages 5 and 6). Braak PD stages 1-3 correspond to incidental Lewy body disease (ILBD), which is considered to represent the presymptomatic PD and/or DLB. In PD and DLB, Lewy bodies and Lewy neurites are distributed throughout the nervous system, including the brain, spinal cord, sympathetic ganglia, enteric nervous system, cardiac and pelvic plexuses, submandibular gland, adrenal medulla and skin. In ILBD, Lewy bodies occur in the brain, spinal cord, sympathetic ganglia, visceral autonomic nervous system and skin. In addition, neuronal loss is found in the substantia nigra, striatum and heart in ILBD. The pathological process of Lewy body disease may target the peripheral and central nervous systems at the same time.
Evolving concepts of globular glial tauopathies

Gabor G. Kovacs
Institute of Neurology, Medical University of Vienna, Vienna, Austria

Recent studies have highlighted a group of 4-repeat (4R) tauopathies that are characterised neuropathologically by widespread, globular, usually Gallyas negative astroglial, and Gallyas positive oligodendroglial inclusions. The overarching term globular glial tauopathy (GGT) has been recommended for three different morphological subtypes distinguished based on the anatomical and cellular (astroglial or oligodendroglial) predominance of pathology. The clinical presentation ranges from behavioral variant of FTD, progressive aphasia, corticobasal syndrome to features of motor neuron disease or other movement disorders. By electron microscopy, oligodendroglial inclusions show granular material and haphazardly oriented filaments. Interestingly occasionally oligodendroglial but not astroglial inclusions can be 3R positive. Neurons show diffuse cytoplasmic immunoreactivity or globular or tangle-like tau immunoreactivity, which also contain the 4R-tau isoform. GGT has been seen also in elderly individuals. Concomitant proteinopathy is not a consistent feature, however, there are cases, which show neuronal and glial TDP-43 lesions in the same affected areas or only in the limbic system as seen for example in Alzheimer disease. Similarity of the oligodendroglial tau pathology to that seen in the α-synucleinopathy multiple system atrophy (MSA) with a different anatomical vulnerability pattern has been noticed. Studies on oligodendroglial response in GGT and MSA show similarities such as loss of nuclear TPPP/p25α immunoreactivity correlating with tract degeneration and enlarged cytoplasmic TPPP/p25α immunoreactivity. However, distinct features, such as more colocalization of α-synuclein than tau with TPPP/p25α can be also recognized. In summary, GGTs represent a peculiar subgroup of neurodegenerative diseases emphasizing the role of the neuroglia in the pathogenesis of these conditions.
Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterized by various combinations of autonomic failure, levodopa-unresponsive parkinsonism, cerebellar ataxia, or pyramidal signs. The histopathological hallmark is the oligodendrocytic glial cytoplasmic inclusions (GCIs) consisting of abnormal alpha-synuclein aggregation (AS). MSA was previously considered three distinct diseases: striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA) and Shy-Drager syndrome. Depending upon the predominant motor symptom, the current consensus criteria for diagnosis of MSA defined two clinical phenotypes: MSA with predominant cerebellar ataxia (MSA-C) and MSA with predominant parkinsonism (MSA-P). Previous studies have reported some cases of MSA patients presenting with severe autonomic failures in the absence of the diagnostic motor signs of MSA, which were referred to as non-motor MSA. These reports have revealed the mild pathological feature of OPCA and SND with the presence of GCIs in vulnerable regions. AS is also found in glial nuclear inclusions (GNIs), neuronal cytoplasmic inclusions (NCIs), neuronal nuclear inclusions (NNIs) and dystrophic neurites. A subgroup of MSA cases with temporofrontal atrophy showed numerous NCIs, particularly in the limbic system. These findings suggest the expanding range of neuronal pathology in MSA. For better understanding of pathological spectrum in MSA, we review the pathological features of the literature and nearly 180 MSA cases in the Brain Resource Center of Institute for Medical Science of Aging, Aichi Medical University.
Pilocytic astrocytoma with anaplastic features

Fausto J. Rodriguez

Division of Neuropathology, Johns Hopkins University School of Medicine

Pilocytic astrocytomas (PA) are well differentiated astrocytic neoplasms representing the most frequent primary brain tumors in children. Numerous studies have demonstrated that a tandem duplication involving the kinase domain of BRAF and leading to a novel fusion (KIAA1549-BRAF) is present in most sporadic PA. PA is assigned a WHO grade I designation given its slow growth potential, long patient survival and potential for cure when totally resected. However, a small subset of PA develop anaplastic changes either de novo or in the setting of prior irradiation. We previously developed diagnostic criteria for these tumors, which included brisk mitotic activity with or without necrosis. These findings were associated with a worse prognosis, akin to diffuse gliomas when compared to historic cohorts. We have also documented frequent PI3K/mTOR activation, in addition to MAPK activation, and deletions involving PTEN and CDKN2A. A recent study by Reinhardt et al. reported a separate molecular methylation class corresponding to a subset reported as anaplastic astrocytoma with piloid features, which is characterized by frequent CDKN2A and ATRX alterations. In the recent update of our experience, we studied 57 resections from 36 patients (23 M, 13 F, mean age 32 years, range 3-75 years). ALT and ATRX loss, as well as alterations involving the MAPK pathway, were frequent. Additionally, a small subset demonstrated H3-K27M mutations. These findings further support the concept that PA with anaplasia is a neoplasm with potential for aggressive clinical course, heterogeneous genetic features and alterations typical of both PA and diffuse gliomas.
Atypical teratoid/rhabdoid tumors arising from gliomas: Histopathological and genetic features of four cases

Junko Hirato¹, Sumihito Nobusawa²

¹Department of Pathology, Gunma University Hospital,
²Department of Human Pathology, Gunma University Graduate School of Medicine

Atypical teratoid/rhabdoid tumor (AT/RT) is a malignant CNS tumor showing rhabdoid cells, polyphenotypic differentiation, and inactivation of SMACB1/INI1 or SMARCA4/BRG1. Most AT/RTs occur de novo; however, they can rarely arise in other tumors. Here, we investigated the histopathological and genetic features of four cases of these tumors, consisting of INI1-deficient rhabdoid cell components and gliomas, to clarify the characteristics of secondary AT/RTs. They included a 27-year-old woman with a para-hippocampal tumor (case 1), a 22-year-old woman with an occipital lobe tumor (case 2), one-year and 11-month-old female infant with a frontal lobe tumor (case 3), and a 24-year-old man with a frontal lobe tumor (case 4). Glioma components of these tumors were pleomorphic xanthoastrocytoma (PXA), anaplastic PXA, low-grade astrocytoma, and ependymoma, respectively. INI1-deficient rhabdoid components of the cases with PXA and anaplastic PXA showed plump eosinophilic cytoplasm, irregular-sized nuclei, and pleomorphism including sickle-shaped nuclei mimicking epithelioid glioblastoma. In case 3, an INI1-deficient component was composed of not only rhabdoid cells, but also epithelioid, pale, and vacuolated cells, resembling de novo AT/RTs. In the results of genetic analysis, FISH analysis detected LOH of 22q in the rhabdoid component of case 1 and both rhabdoid and lower-grade components in the tumors of cases 2 and 4. Direct sequencing for the INI1 mutation identified only the AT/RT component of case 3. Histological features of secondary AT/RTs may be different from de novo AT/RT depending on paternal tumors. There is a possibility that the genetic status of INI1 also affects morphological features.
Diffuse midline gliomas: An update

Chitra Sarkar, Kavneet Kaur, Anupam Kumar, Pankaj Pathak, Vaishali Suri, Mehar Chand Sharma, Ajay Garg, Ashish Suri

Department of Pathology, All India Institute of Medical Sciences (AIIMS), New Delhi

Diffuse midline gliomas (DMG), recognized as a new diagnostic entity in the updated 2016 WHO classification, are infiltrative midline high grade gliomas, which harbour K27M mutation in histone genes, H3F3A or HIST1H3B/C. They occur predominantly in children (median age 5-11 years), but can also be seen in adults. These tumors involve midline structures, the most common locations being brainstem, thalamus and spinal cord. They exhibit a wide morphological spectrum with features overlapping nearly all histological variants of astrocytic tumors. These are aggressive grade IV tumors with 2 year survival rate of around 10%. The use of H3K27M mutant specific immunohistochemistry is useful to identify the mutation and therefore very helpful for the diagnosis of this entity. In our own series of 46 midline astrocytic tumors, 60% were H3 K27M mutant. Distinct differences were noted between adult and pediatric midline gliomas as well as H3 K27M mutant and wild type midline gliomas. Clinical outcome of the mutant cases was significantly worse. Interestingly, the same mutation has recently been observed in many other tumors such as ependymomas and pilocytic astrocytomas, with no distinct prognostic significance. For these reasons, the Working Committee 3 (cIMPACT NOW update 2) have provided diagnostic clarifications for this entity viz. that the term diffuse midline glioma, H3 K27M mutant should be reserved for tumors that are diffuse (i.e. infiltrating), midline (thalamus, brainstem, spinal cord etc.), gliomas and H3K27M mutant, and should not be applied to other tumors that are H3 K27M mutant.
Anaplastic Pleomorphic Xanthoastrocytoma

Maysa A. Al-Hussaini

Department of Pathology and Laboratory Medicine, King Hussein Cancer Foundation, King Hussein Cancer Center

Pleomorphic xanthoastrocytoma (PXA) is a well categorized brain tumor that affects children and young adults. It primarily presents with seizure and a cystic lesion with mural nodule centered in the cortex, most commonly in the temporal lobe, is the classical radiological finding. It is associated with prolonged survival if completely excised and is assigned a grade II by the WHO. Anaplastic PXA (aPXA) has recently been officially recognized as a grade III tumor and appears as a distinct entity in the 2016 WHO Classification of Tumours of the CNS. To be eligible for aPXA, the tumor should have an excess of mitotic figures (≥ and > 5 mitoses/10 HPFs). The presence of the necrosis is an additionally, but none core criteria. aPXA is associated with dismal outcome. The recent association of PXA with BRAF V600E mutation has opened the door for a better control of the tumors with potential response to targeted therapies. Testing for BRAF V600E mutation has become a cornerstone in the management of PXA and aPXA cases. The differential diagnosis for aPXA includes other high grade gliomas, especially glioblastoma (GBM). The relation of aPXA with GBM, in particular epithelioid GBM, especially in view of the BRAF V600E mutation in the latter will be discussed.
Molecular mechanisms underlying mammalian-specific neocortical development and evolution

Tadashi Nomura
Department of Developmental Neurobiology, Kyoto Prefectural University of Medicine

The mammalian neocortex is a conspicuous brain structure characterized by a six-layered laminar organization. During neocortical development, excitatory projection neurons migrate toward the brain surface by changing their shapes from multi-polar to bi-polar morphology, which accomplishes an inside-out pattern of cortical development. Deleterious changes in genetic and environmental factors significantly affect neuronal migration and consequence congenital cortical abnormalities. In contrast, a six-layered neocortex does not develop in non-mammalian species: all neurons exhibit multi-polar shape and organize a three-layered dorsal cortex in reptiles. However, molecular mechanisms underlying species-specific neuronal migration and cortical organization remain unclear. Here we identify that species-dependent regulation of Wnt signaling plays an essential role in mammalian and reptilian corticogenesis. Temporal controls of Wnt signaling in migratory neurons are crucial for multipolar-to-bipolar conversion in mammals, and manipulation of Wnt signaling activity phenocopied species-specific neuronal morphologies. We suggest that heterochronic changes in Wnt activity contributed to the evolution of mammalian-type neuronal migration and an inside-out pattern of corticogenesis.
Hippocampal neurogenesis during development and aging in human

Homa Adle-Biassette\textsuperscript{1,2,3}, Sara Cipriani\textsuperscript{2}, Isidre Ferrer\textsuperscript{4}, Eleonora Aronica\textsuperscript{5}, Gabor Kovacs\textsuperscript{6}, Philippe Manivet\textsuperscript{2,3}, Pierre Gressens\textsuperscript{2}

\textsuperscript{1}Department of Pathology, Lariboisiere Hospital, APHP, Paris, France, \textsuperscript{2}PROTECT, INSERM, Paris Diderot University, Sorbonne Paris Cite, F- 75019 Paris, France, \textsuperscript{3}Plateforme de Bio-Pathologie et de Technologies Innovantes en Sante, Centre de Ressources Biologiques, BB-0033-00064, Lariboisiere Hospital, APHP, Paris, France, \textsuperscript{4}Department of Pathology and Experimental Therapeutics, University of Barcelona, Bellvitge Campus, \textsuperscript{5}Department of (Neuro) Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, \textsuperscript{6}Institute of Neurology, Medical University of Vienna, Vienna, Austria

The main steps of the formation of the DG have been largely studied in rodents. Adult neurogenesis remains controversial in human. We characterized the progenitor subtypes, cell fate molecules and the dynamics of neurogenesis of the human hippocampal formation from the embryonic period to adulthood, including in patients with Alzheimer's disease (AD). The Ammon's horn includes two germinal compartments, the ventricular zone containing ventricular radial glial cells (RGC) and the subventricular zone containing unipolar RGC cells and TBR2-positive intermediate progenitor cells (IPC). Pyramidal layers are generated with the "inside-out" pattern but show differences in layer segregation between the ammonic and subicular plates. RGC density declines with neurogenesis from mid-gestation until the perinatal period. The DG forms from two matrices. The secondary dentate matrix surrounds the dentate anlage and contains unipolar and multipolar RGC and IPC. By GW16, when the granule cell layer can be delineated, a hilar matrix and the subgranular zone (SGZ) become identifiable containing unipolar RGC and IPC. Dentate neurons are generated with the "outside- in" pattern. Around the perinatal period, the dense network of RGCs in the SGZ starts to decrease in density, but neurogenesis persists during childhood, few Doublecortin-positive cells are seen in adults. The DG of both control and AD individuals shows Nestin-positive and/or GFAP-delta-positive cells displaying different morphologies. In conclusion, pools of morphologically, antigenically, and topographically diverse neural progenitor cells are present from early developmental stages until adulthood, including in AD patients, while their neurogenic potential seems minor in the adult. Supported by European Commission FP7-HEALTH-2011-2.2.2-2/Develage
Fetal CNS is remarkably developing in the first trimester and changing its appearance from premature tubal structure to the bilateral cerebri, cerebellum and brainstem. Neurosonoembryology has been improved with great advances of 3D ultrasound technology such as HDlive silhouette technology and studio-live technology. However, detectable CNS abnormalities are limited in the first trimester because neuronal migration and proliferation will take place from 3rd or 4th months of gestation. From the early second trimester, the brain structure is clearly observed by ultrasound and most of congenital brain anomalies can be detected but it is quite hard to detect neuronal migration disorders during pregnancy. Phenotype of migration disorders in the cortex conspicuously appears after 28 weeks of gestation when cortical gyration/sulcation is clearly visualized. It has been believed that it is quite hard to detect migration disorder before 28 weeks. However, in most cases with neuronal migration disorder, neurological prognosis is not favorable. "Early detection of migration disorder before gyration" is one of our important missions. From our experience, early diagnoses of migration disorder have been possible by using transvaginal high-resolution 3D ultrasound from early second trimester by observation of Sylvian fissure appearance, abnormal early sulci, irregular ventricular wall, and persistent ganglionic eminence. Close observation of those brain structural changes in detail is not generally performed however it might help to establish a new field of fetal neuroscience.
A continuing role for morphology in a multidisciplinary environment

Brian Harding\textsuperscript{1,2}

\textsuperscript{1} University of Pennsylvania, \textsuperscript{2} Department of Pathology, Children's Hospital of Philadelphia

Advances in medical imaging and genetic knowledge have become so impressive of late that there is a tendency to neglect the acquisition of detailed histomorphologic information. A variety of examples taken from my personal practice, both with and without genetic diagnosis or specific imaging features, will serve to demonstrate the continuing importance of neuropathologic studies in defining new entities and formulating pathogenetic hypothesis. In the past a disorder was often first categorized in morphologic terms; but even today, neuropathologic findings may herald the emergence of a novel disorder when clinical and imaging studies are inconclusive and genetic information lacking. Reference will be made to both published and unpublished case material that reflects this situation.