

O10-1

Expression of GLUT1 on pseudopalisading cells and perivascular tumor cells: an independent prognostic factor of patients with glioblastomas

Satoru Komaki¹, Takuya Furuta¹, Kyouhei Yamada¹, Naohisa Miyagi², Hideo Nakamura², Motohiro Morioka², Yasuo Sugita¹

¹Department of Pathology, Kurume University School of Medicine, Kurume, Japan,

²Department of Neurosurgery, Kurume University School of Medicine, Kurume, Japan

Glucose Transporter-1 (GLUT1) is a 492-amino-acid membrane peptide and expressed in endothelial cells of blood brain barrier and a uniporter protein in humans encoded by the SLC2A1 gene. GLUT1 is essential for central nervous system because glial and neuronal cells are dependent on the energy source in glycometabolism. GLUT1 was expressed in various carcinomas and may play an important role in glycometabolism of malignant neoplasms. In order to clarify the role of GLUT1 in glioblastoma, the present study assessed the expression and localization of GLUT1 in consecutive 52 glioblastomas using immunohistochemical analysis and SLC2A mRNA using in situ hybridization. Immunohistochemically, GLUT1 expressed mainly expressed at the cell membrane of perivascular and pseudopalisading tumor cells. GLUT1 expression of cases divided into high expression group and low expression group as a result of immunohistochemical findings. All cases expressed GLUT1 in various degrees, and 16 (30.8%) cases showed strong intensity and high proportion of the tumor cells. SLC2A mRNA was also expressed more highly high expression group than low expression group. A Kaplan-Meier survival analysis revealed that GLUT1 high expression group showed lower overall survival rate than low expression group (log-rank test, $p=0.001$). MIB-1 labeling index of GLUT1 high expression group was higher than that of low expression group. These results indicated that expression of GLUT1 in tumor cells enhance glycolysis and migration of glioblastomas and the correlation with the patient's prognosis.

O10-2

Oncogene addiction switch from NOTCH to PI3K/AKT require simultaneous targeting of NOTCH and PI3K pathway inhibition in glioblastoma

Norihiko Saito, Kazuya Aoki, Nozomi Hirai, Ryo Suzuki, Satoshi Fujita, Kenichiro Sato, Haruo Nakayama, Morito Hayashi, Takatoshi Sakurai, Satoshi Iwabuchi

Department of Neurosurgery, Toho University Ohashi Medical Center

Notch signaling pathway regulates normal stem cells in the brain and glioma stem cells (GSCs). However, blocking the proteolytic activation of NOTCH with γ -secretase inhibitors (GSIs) fails to alter the growth of some GSCs as GSIs seem to be active in only a fraction of GSCs lines with constitutive NOTCH activity. Here we report loss of PTEN as a critical event leading to resistance to NOTCH inhibition, which causes the transfer of oncogene addiction from the NOTCH to the phosphoinositol-3 kinase (PI3K)/AKT pathway. We investigated the effects of Notch inhibition in GSC using GSI. Drug cytotoxicity test on 16 GSCs show differential growth response to GSI stratifying GSCs into two groups: responders (6 cell lines) vs non-responders (10 cell lines). Active Notch signaling seems to be important features for the GSC as Notch inhibition only affected GSCs defined as having increased Notch activity. However in the responder group GSCs with the PTEN mutation seems to be less sensitive to GSI treatment. Here we show that NOTCH regulates the expression of PTEN and the activity of the PI3K/AKT signaling pathway in GSCs since treatment with GSI attenuated Notch signaling and increases PTEN expression. NOTCH regulates PTEN expression via Hes-1 as knockdown of either Notch or Hes1 led to increase expression of PTEN. This novel observation suggests the need to simultaneous inhibition of both pathways as a means to improve therapeutic efficacy in human GBMs.

O10-3

Development of a novel FISH probe for detection of 1p/19q codeletion in routine glioma diagnosis

Kaishi Satomi¹, Kai Yamasaki^{2,3}, Akihiko Yoshida¹, Susumu Wakai¹, Yuko Matsushita⁴, Yoshitaka Narita⁴, Takashi Komori⁵, Ryo Nishikawa⁶, Keisuke Ueki⁷, Koichi Ichimura²

¹ Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan,

² Division of Brain Tumour Translational Research, National Cancer Center Research Institute, Tokyo, Japan,

³ Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan,

⁴ Department of Neurosurgery and Neurooncology, National Cancer Center Hospital, Tokyo, Japan,

⁵ Department of Laboratory Medicine and Pathology (Neuropathology), Tokyo Metropolitan Neurological Hospital, Tokyo, Japan,

⁶ Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Saitama, Japan,

⁷ Department of Neurosurgery, Dokkyo University School of Medicine, Tochigi, Japan

The World Health Organization Classification of Tumours of the Central Nervous System (2016) has introduced integrated phenotypic and genotypic criteria to define diffuse glioma entities. Diagnosis of oligodendroglioma requires demonstration of 1p/19q codeletion. The analysis is commonly carried out using fluorescence in situ hybridisation (FISH). However, we need to be aware of potential methodological and interpretational pitfalls as some commercially available probes hybridise to loci at 1p36 or 19q13 and detect partial loss of these regions, which is a common feature of glioblastomas. To improve diagnostic accuracy of 1p/19q FISH, we have developed a novel FISH probe sets. They are designed to hybridise to 1p31 and 19q13.1, the loci rarely deleted in non-oligodendroglial tumours. Ten diffuse glioma formalin-fixed paraffin-embedded (FFPE) samples (two oligodendrogliomas, three anaplastic oligodendrogliomas, one diffuse astrocytoma, and four anaplastic astrocytomas) were examined. The 1p/19q status of all samples was validated by multiplex ligation-dependent probe amplification (MLPA) with corresponding frozen tissues. For FISH analysis, clear and bright target and control signals were detected in nine out of ten FFPE samples. Four oligodendroglial tumours lost a target signal yielded one red target signal and two green control signals. All astrocytic tumours showed balanced red and green signals. Our FISH results thus showed perfect concordance with the MLPA results and correctly identified 1p/19q codeleted tumors. Thus, we have successfully developed a novel FISH probe sets for detection of 1p/19q codeletion. A validation using a large number of various gliomas with known 1p/19q status determined by MLPA is underway.

O10-4

BCL2 expression is associated with a poor prognosis independent of cellular origin in primary central nervous system diffuse large B-cell lymphoma

Keishi Makino¹, Naoki Shinojima¹, Jun-ichiro Kuroda¹, Shigetoshi Yano¹, Yoshiki Mikami², Akitake Mukasa¹

¹Department of Neurosurgery, Kumamoto University, Kumamoto, Japan,

²Department of Diagnostic Pathology, Kumamoto University Hospital, Kumamoto, Japan

【Purpose】 Primary central nervous system diffuse large B-cell lymphoma (CNS-DLBCL) is a distinct clinicopathological entity with a poor prognosis. Concurrent MYC and BCL2 overexpression predicts inferior prognosis in systemic DLBCL, although their prognostic significance remains unclear in primary CNS-DLBCL. **【Methods】** Pretreatment diagnostic biopsy samples were retrospectively evaluated for 79 patients with primary CNS-DLBCL who were treated between January 2001 and December 2017. Histological and immunohistochemical testing were performed to evaluate the patients' statuses for various markers, which were also evaluated for associations with survival outcomes. **【Results】** According to the Hans criteria, 26 patients (32.9%) had the germinal center B-cell subtype and 53 patients (67.1%) had the activated B-cell subtype. Forty-one cases (51.9%) were positive for MYC (expression of over 40%), 33 cases (41.8%) were positive for BCL2 (expression of over 70%), 22 patients (27.8%) were positive for both MYC and BCL2, and 27 patients (34.2%) were negative for both MYC and BCL2. There were no significant differences in survival between the germinal center and activated B-cell subtypes. Furthermore, MYC positivity was not associated with overall survival ($p=0.369$) or progression-free survival ($p=0.253$). However, BCL2 positivity was significantly associated with poor overall survival ($p=0.039$) and progression-free survival ($p=0.036$). Co-expression of MYC and BCL2 was not associated with survival. **【Conclusion】** Our data suggest that evaluating BCL2 expression may help predict the prognosis in cases of primary CNS-DLBCL.

O10-5

Serum IL-2 receptor and random skin biopsy for intravascular large B-cell lymphoma - cases with central nervous system involvement are particular for these diagnostic methods ? -

Eiichi Ishikawa¹, Erika Yamada¹, Rei Watanabe², Hideaki Matsumura¹, Noriaki Sakamoto^{1,3}, Masahide Matsuda¹, Takao Tsurubuchi¹, Shingo Takano¹, Makoto Shibuya⁴, Akira Matsumura¹

¹Departments of 1 Neurosurgery, Faculty of Medicine, University of Tsukuba,

²Departments of Dermatology, Faculty of Medicine, University of Tsukuba,

³Departments of Diagnostic Pathology, Faculty of Medicine, University of Tsukuba, Tsukuba,,

⁴Central laboratory, Hachioji medical center, Tokyo medical university

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal B-cell lymphoma which affects blood vessel lumina in all organs including brain. A number of researchers proved usefulness of random skin biopsy for diagnosis of IVLBCL. We retrospectively analyzed data of 21 patients with suspected IVLBCL (7 cases with central nervous system (CNS) involvement and 14 cases without CNS involvement) who underwent single or dual skin biopsies (5 cases) and random skin biopsies (16 cases). As a result, 16 cases including 6 CNS involvement cases out of 21 patients were diagnosed with IVLBCL. In 16 cases with random skin biopsy, the sensitivity, specificity and positive predictive value (PPV) of the random skin biopsy were 69.2%, 100% and 100%, respectively. In cases with data of both skin biopsies and plasma soluble interleukin-2 receptor (sIL-2R), there was significant correlation between tumor-positive ratios of biopsy samples and sIL-2R values. There was no difference in relationship of these diagnostic methods between CNS involvement and non-involvement groups, although most of CNS involvement group had steroid use before diagnosis. In conclusion, the random skin biopsy should be applied for IVLBCL suspected patients before brain biopsy even in patients with CNS involvement, although this method has false-negative result in low sIL-2R cases especially steroid use.

Pathological spreading of TDP-43 studied in real time: Impaired microglia function leads to propagation of TDP-43 along the axon and into surrounding tissue

Adam J Svahn¹, Emily K Don¹, Rowan Radford¹, Nicholas J Cole¹, Albert Lee^{1,2}, Justin Yerbury³, Manuel B Graeber⁴, Roger S Chung¹, Marco Morsch¹

¹ Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, North Ryde, NSW, Australia,

² Australian Proteome Analysis Facility, Macquarie University, North Ryde, NSW 2109, Australia,

³ School of Biological Sciences, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, New South Wales, Australia,

⁴ Brain Tumour Research Laboratories, Brain and Mind Centre, University of Sydney, Sydney, Australia

Introduction: TDP-43 has been identified as the signature protein of the pathological inclusions that characterise amyotrophic lateral sclerosis (ALS/MND) and frontotemporal dementia (FTLD). The goal of this project was to evaluate whether microglia phagocytose TDP-43 originating from dying motor neurons and whether such phagocytosis of TDP-43 may be neuroprotective.

Methods: We examined the distribution and release of human (h)-TDP-43 *in vivo* in the zebrafish spinal cord in the presence and absence of microglia. We developed a technique (UV-mediated neuronal injury) to selectively injure individual motor neurons expressing fluorescent hTDP-43. We were able to observe the fate of TDP-43 and the response of nearby microglia in real time at the single-cell level. Antisense morpholino injections of pu1 allowed us to deplete the phagocyte population selectively.

Results: Following neuronal injury, we observed a reproducible pattern of neurodegeneration that results in cellular rupture and microglial clearance of TDP-43. In contrast, when microglia were impaired, injured neurons showed a delayed demise characterized by cytoplasmic mislocalisation, somatofugal leakage and axonal spreading of TDP-43. Furthermore, we occasionally observed TDP-43 accumulation in surrounding tissue.

Conclusions: Our data provides novel insights into the mechanisms underlying TDP-43 pathogenicity and suggest a protective role for microglia early on during neurodegeneration. It suggests that disruption of microglial uptake leads to cytoplasmic accumulation and spreading of TDP-43. Thus, we propose that the pathological load of TDP-43 in ALS/FTLD may be a direct consequence of microglial functional insufficiency, being unable to cope with the amount of neuronal debris that accumulates during disease progression.

O11-2

Splicing Repression is a Major Function of TDP-43 in Motor Neurons

Liam Chen, Philip Wong

Department of Pathology, Johns Hopkins Hospital

Nuclear depletion of TDP-43, an RNA binding protein which represses aberrant splicing, may underlie neurodegeneration in amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD). As multiple functions are ascribed to TDP-43, its major role(s) that may be compromised in ALS/FTD remains unknown. Using *Drosophila* and murine models lacking TDP-43 in motor neurons, we show that TDP-43 mediated splicing repression is central to motor neuron physiology. Employing an AAV9 approach to deliver a chimeric protein comprised of the RNA recognition domain of TDP-43 fused to an unrelated splicing repressor (RAVER1), we validate TDP-43 splicing repression in the motor neuron as a therapeutic target. We establish that splicing repression is a principal role of TDP-43 in motor neurons and identify a novel mechanism-based therapeutic target for ALS.

HSF1 suppresses adenovirus-induced neuronal TDP-43 aggregate formation in culture

Kazuhiko Watabe¹, Yoichiro Kato², Miho Sakuma³, Makiko Murata¹, Motoko Niida², Akiyoshi Kakita⁴, Noriyuki Shibata²

¹ Department of Medical Technology (Neuropathology), Kyorin University Faculty of Health Sciences,

² Department of Pathology, Tokyo Women's Medical University,

³ School of Medicine, Tokyo Women's Medical University,

⁴ Department of Pathology, Brain Research Institute, Niigata University

Introduction: TAR DNA-binding protein 43 (TDP-43) is a main constituent of cytoplasmic aggregates in neuronal and glial cells in cases of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). We have previously demonstrated neuronal cytoplasmic aggregate formation induced by recombinant adenoviruses expressing human wild type (WT) and C-terminal fragment (CTF) TDP-43 under the condition of proteasome inhibition in vitro and in vivo. In the present study, we examined whether heat shock response affects adenovirus-induced TDP-43 aggregate formation in vitro.

Methods: The 1464R rat neural stem cells were differentiated into neurons in the presence of retinoic acid, and co-infected with adenoviruses expressing DsRed-tagged human WT and CTF TDP-43, and EGFP-tagged human heat shock transcription factor 1 (HSF1), a master regulator of heat shock response, and candidate downstream heat shock proteins, i.e., heat shock protein 70 (HSP70), DNAJB2a/b, HSPB8, and HSPH3 in the presence of proteasome inhibitor MG-132.

Results: Two days in vitro, DsRed-positive, RIPA-insoluble cytoplasmic aggregates containing phosphorylated TDP-43 were formed in TDP-43 adenovirus-infected and MG-132-treated TuJ1-positive neurons as revealed by immunofluorescence and western blot analysis. Co-infection of HSF1 adenovirus markedly suppressed formation of the TDP-43 aggregates. However, adenoviruses expressing HSP70, DNAJB2a/b HSPB8, and/or HSPH3 failed to suppress TDP-43 aggregate formation.

Conclusion: These results suggest HSF1 as a potential therapeutic application for preventing TDP-43 aggregate formation in ALS and FTLD. Further studies are required to identify candidate molecules, other than HSP70, DNAJB2a/b, HSPB8, and HSPH3, locating downstream of HSF1 to counteract TDP-43 aggregate formation.

Early onset amyotrophic lateral sclerosis associated with a TARDBP S375G variant: neuropathologic characterization and neurobiologic studies

Kathy L Newell¹, Francesca Paron², Jill Murrell³, Elisa Salis², Cristiana Stuani², Maurizio Romano⁴, Bernardino Ghetti³, Emanuele Buratti²

¹Dept of Pathology & Laboratory Medicine, University of Kansas School of Medicine, Kansas City, KS, US,

²International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy,

³Dept of Pathology & Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, US,

⁴Dept of Life Sciences, University of Trieste, Trieste, Italy

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with usual onset in midlife. We are studying the brain and spinal cord from a 26 year-old woman who developed clinical symptoms of ALS at age 22. A clinical history of ALS is reported in distant relatives. Histological sections were stained with Luxol fast blue-H&E and immunohistochemically with TDP-43 antibodies. Neuropathologic evaluation confirmed upper and lower motor neuron loss, corticospinal tract degeneration, and denervation atrophy of skeletal muscle. TDP-43 immunoreactive neuronal and glial aggregates were present in motor cortex, globus pallidus, putamen, thalamus, substantia nigra, inferior olivary nucleus, and anterior horns. DNA analysis of the *TARDBP* gene identified a S375G change, predicted to affect post-translational modification with elimination of a TDP-43 protein phosphorylation site. A C9ORF72 expansion was not identified. The S375G variant was listed as low frequency in general population sequencing databases and reported in one 41 y/o patient with sporadic ALS. To determine whether this variant is pathogenic, we studied recombinant S375G protein in functional assays. In cultured cells, S375G expression was toxic, significantly more localized to the nucleus than wild-type TDP-43, and displayed significant increase in nuclear localization with respect to neighboring TDP-43 mutations. A “phosphomimic” mutation, introduced to study the effect of loss of an endogenous TDP-43 phosphorylation site, showed significantly altered TDP-43 nuclear-cytoplasmic distribution. This finding suggests an important pathophysiologic role for TDP-43 phosphorylation in certain disorders. More studies of potentially pathogenic TDP-43 variants, often reported in association with sporadic ALS or of unknown significance, are needed.

O11-5

poly-GR c9RANT correlate with neurodegeneration and clinicopathological phenotype in C9ORF patient

Nobutaka Sakae, Kevin F Bieniek, Yong-Jie Zhang, Kelly Ross, Tania F Gendron, Melissa E Murray, Rosa Rademakers, Leonard Petrucelli, Dennis W Dickson

Department of Neuroscience, Mayo Clinic Jacksonville

Introduction: An expanded GGGGCC hexanucleotide repeat in C9ORF72 is the most common genetic cause of frontotemporal lobar degeneration (FTLD) and motor neuron disease (MND). The pathomechanism of C9ORF72 pathology is unclear. Growing evidence from cell culture and animal model studies suggest the arginine containing poly-PR and poly-GR of the C9ORF72 repeat-associated non-ATG translated (C9RANT) dipeptide repeat polymers have distinct toxicity among the five C9RANTs. In human autopsy brain, however, the mechanism of poly-GR toxicity is not fully understood. **Methods:** We analyzed sense strand C9RANTs (poly-GA, GP and GR) and asymmetric dimethyl arginine (aDMA) pathology in brains of 40 patients with C9ORF72 mutation using unbiased digital image analysis. We also studied overexpression of GFP-tagged C9RANTs in HEK293 cells. **Results:** The burden of poly-GR neuronal cytoplasmic inclusion (NCI) was associated with neurodegeneration and c9FTLD/MND subtype in hippocampus and frontal cortex. Further, aDMA pathology was correlated with poly-GR NCI and preferentially co-localized with poly-GR NCI. The in vitro studies suggested that aDMA modification of poly-GR contributes to formation of poly-GR cytoplasmic inclusions and gain of toxicity of poly-GR. **Conclusion:** We found that poly-GR NCI burden correlates with neurodegeneration in C9FTLD/MND patients. The distribution of poly-GR NCI and aDMA NCI were highly correlated. Neuropathological studies and in vitro assays suggested that gain of toxicity of poly-GR might be associated with aDMA modification. Our study provides novel insights into the contribution of poly-GR toxicity towards neurodegeneration of C9FTLD/MND.

An autopsy case of hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P, or HMSN Okinawa type)

Shugo Suwazono^{1,2}, Tomoyasu Matsubara³, Ryo Nakachi², Eriko Atsumi⁴, Yuishin Izumi⁵,
Miwako Kido², Takashi Tokashiki², Ryuuji Kaji⁵, Mari Yoshida⁶, Shigeo Murayama³

¹ Center for Clinical Neuroscience, National Hospital Organization Okinawa Hospital,

² Department of Neurology, National Hospital Organization Okinawa Hospital,

³ Brain Bank for Aging Research, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology,

⁴ Department of Pathology, National Hospital Organization Okinawa Hospital,

⁵ Department of Clinical Neuroscience, Institute of Biomedical Sciences, Tokushima University Graduate School,

⁶ Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University

Introduction: Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN Okinawa type; HMSNO, OMIM # 604484, or HMSN-P, as used in the first detailed report [Takashima, 1997]), is a motor and sensory neuronopathy with autosomal dominant inheritance, adult onset, and slowly progressive course [Fujisaki, 2018]; it is associated with a mutation in TRK-fused gene (TFG) [Ishiura, 2012]. This disease might serve as a good example for considerations of the pathomechanisms of neurodegenerative disorders whose proposed etiologies are caused by one gene mutation; therefore, detailed pathological examination is very important. **Clinical summary:** The patient exhibited painful muscle cramps and weakness of the lower extremities at the age of 44; this lower extremity weakness gradually worsened, such that, fifteen years later, she was unable to walk and was admitted to our hospital. Prominent fasciculations on all extremities, proximal dominant muscle weakness, and mild superficial sensory impairment were observed; deep tendon reflexes were diminished and no pathological reflexes were present. Non-invasive positive pressure ventilation was initiated at the age of 70; tracheostomy was performed at the age of 74. Gastrostomy was implemented at the age of 80; the patient died at the age of 80, due to sepsis following pneumonia. **Pathological findings:** Upper and lower motor neuron analysis showed cellular loss. Anti-TFG antibody and anti-phosphorylated TDP-43 antibody staining revealed positive intracellular granules. **Conclusion:** Pathological findings in this case confirmed the characteristic findings reported in HMSN-P previously [Takashima, 1997, Fujita, 2011].

Novel patient-derived primary central nervous system lymphoma xenograft models to exploit therapeutic target

Yohei Miyake¹, Kensuke Tateishi¹, Taishi Nakamura¹, Akio Miyake², Yuko Matsushita³, Hidetoshi Murata¹, Shoji Yamanaka², Tetsuya Yamamoto¹, Koichi Ichimura³

¹Department of Neurosurgery, Yokohama City University, Yokohama, Japan,

²Department of Pathology, Yokohama City University, Yokohama, Japan,

³Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan

【Introduction】 The large-scaled gene analyses revealed that chronic activation of NF- κ B signaling pathway, mainly caused by *CD79B* or *MYD88* mutation, played a crucial role on tumorigenesis of primary central nervous system lymphoma (PCNSL). Recently, several targeting drugs for the NF- κ B signaling pathway, such as ibrutinib (BTK inhibitor), have been discovered. To elucidate the molecular and biological mechanism of PCNSL, highly-reproducible animal models is important. However, the establishment of PCNSL animal models is considered to be difficult, because little patient-derived PCNSL cell lines have been reported. In this study, we attempted to establish patient-derived PCNSL cell line based on our experiences to create glioblastoma stem like tumorsphere models.

【Method】 After surgical biopsy, PCNSL cells were implanted to the immunodeficient mice brain. Once tumor was harvested, pathological and genetic analyses were performed to confirm their reproducibility between patient specimens and patient-derived cell lines.

【Results】 Of note, we successfully established 7 xenograft models (patient-derived PCNSL cell lines) out of 9 cases. In all 7 cases similar pathological characteristics was observed. Immunohistochemical analysis demonstrated positive expression of B-cell markers, including CD20 and CD79a. DNA fingerprinting revealed matched DNA identification. Besides, we confirmed *CD79B* and *MYD88* mutation were completely inherited to the cell lines. Sensitivity of ibrutinib and methotrexate were variable in each cell line. Currently, we are performing the comprehensive genome analysis using the target sequence panel.

【Conclusion】 We established the largest panels of patient-derived PCNSL xenograft models, which would develop future preclinical investigations.

Clinicopathological study of diffuse large B-cell lymphoma associated with chronic inflammation arising in the CNS

Yasuo Sugita, Takuya Furuta, Satoru Komaki, Hiroko Muta, Mayuko Moritsubo, Kouichi Ohshima

Department of Pathology, University of Kurume, Kurume, Japan

【Introduction】 Diffuse large B-cell lymphoma associated with chronic inflammation (DLBCL-CI) is a lymphoma occurring in the setting of longstanding chronic inflammation and showing association with EBV. DLBCL-CI involving the CNS is, however, rare, and the features are not well characterized. **【Methods】** We assessed clinicopathological features of 4 DLBCL-CI cases. **【Clinical results】** MRIs showed a solid and a cystic lesion (case 1, 66 yr, female), or a cystic lesion in the posterior fossa (case 2, 57 yr, female), respectively and a left frontal (case 3, 96 yr, male), or a right frontal-temporal (case 4, 77 yr male), subdural lesion, respectively. Aggressive clinical courses were recorded in cases 1 and 3, and 2 patients remained in remission (cases 2, 4), respectively. **【Pathological results】** In case 1, the solid lesion showed a proliferation of atypical lymphocytes, and the cystic lesion showed keratinous debris, which was consistent with an epidermoid cyst (EC). In case 2, the cystic lesion was consistent with an EC. Additionally, atypical lymphocytes were scattered adjacent to an EC without forming a mass. In case 3, atypical lymphocytes conglomerated in the thick outer membrane (TOM) and subdural space of chronic subdural hematoma (CSH) and invaded brain parenchyma. In case 4, atypical lymphocytes conglomerated in only TOM of CSH. In all cases, atypical cells were EBV positive and in the fibrin background. **【Discussion】** Fibrin-associated EBV-positive DLBCL (FDLBCL) has been reported as the variant of DLBCL-CI with favorable prognosis. Therefore, cases 2, 4 might be consistent with FDLBCL of the CNS.

012-3

HMGA2 is a prognostic factor associated with malignant phenotype in medulloblastoma

Yoshiki Arakawa, Bin Liu, Yukinori Terada, Yasuzumi Matsui, Etsuko Hattori, Sosuke Sumiyoshi, Nobuyuki Fukui, Masahiro Tanji, Yohei Mineharu, Susumu Miyamoto

Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

Medulloblastoma is the most common of the embryonal tumor arising in the cerebellum. The molecular mechanism of its oncogenesis has been revealed by recent studies. The constitutive expression of high mobility group AT-hook 2 (HMGA2) is associated with a highly malignant phenotype and reduced survival in several malignancies. However, little is known about the clinical and biological significance of HMGA2 in medulloblastoma. In this study, we explore the expression, prognostic and therapeutic role of HMGA2 in medulloblastoma. HMGA1 and HMGA2 expressions were examined using immunohistochemistry in 20 patients with medulloblastoma. To examine the function of HMGA2 expression, knock-down HMGA2 expression was applied in Daoy, D283 and D341 cells. Overexpressions of HMGA1 and HMGA2 were frequently identified in medulloblastoma tissues. In addition, high expression of HMGA2 correlated with high proliferation marker Ki-67 labeling index. High expression of HMGA2 was significantly associated with progression free survival and overall survival of patients with medulloblastoma ($p=0.021$ and $p=0.016$, respectively). Functional experiments confirmed that knock-down of HMGA2 resulted in inhibited cell proliferation, migration/invasion and enhanced apoptosis in vitro. In conclusion, HMGA2 overexpression is frequent in medulloblastoma, and its expression is related to proliferation marker and poor prognosis.

The correlation of fluorescence of protoporphyrinogen 9 and molecular biological characters in gliomas

Shigeo Ohba¹, Kazuhiro Murayama², Syunsuke Nakae¹, Eriel Sandika³, Yuya Nishiyama¹, Hikaru Sasaki³, Seiji Yamada⁴, Masato Abe⁵, Mitsuhiro Hasegawa¹, Yuichi Hirose¹

¹ Department of Neurosurgery, Fujita Health University, ² Department of Radiology, Fujita Health University,

³ Department of Neurosurgery, Keio University, ⁴ Department of Pathology, Fujita Health University,

⁵ Department of Pathology, School of Health Sciences, Fujita Health University

To increase the extent of resection of gliomas, several methods such as use of 5-aminolevulinic acid (5-ALA) have been performed. The correlation of intraoperative fluorescence and several clinical, radiographies, molecular biological and histopathological characters were evaluated. Total 104 patients of gliomas, including 53 males and 51 females were evaluated. The mean age was 54.2 years. Intraoperative fluorescence was observed in 78.8% of cases. Older age, enhanced cases, and high CBV were revealed to be associated with intraoperative fluorescence. The rate of intraoperative fluorescence in World Health Organization (WHO) grade 2, 3, and 4 tumors was 26.3%, 76.9%, and 96.6%, respectively. The MIB-1 index in the tumor with intraoperative fluorescence was significantly higher than in non-fluorescence tumors. The positive rate of intraoperative fluorescence in gliomas harboring wildtype isocitrate dehydrogenase (IDH) is significant higher than that in gliomas harboring mutant IDH. Limited to WHO grade 2 and 3 tumors, the positive rate of intraoperative fluorescence in gliomas harboring wildtype IDH tumors tend to be higher than that in gliomas harboring mutant IDH. In vitro assay revealed that artificial glioma cells transformed by mutant IDH showed less amount of exogenous 5-ALA derived protoporphyrinogen 9(Pp9) compared to artificial glioma cells transformed by H-Ras. There was the difference in the expression of mRNA of enzymes associated with the metabolites of 5-ALA between them. These results suggested that mutant IDH affected the amount of Pp9 indirectly, which contributed to the less intraoperative fluorescence in gliomas harboring mutant IDH compared to gliomas without mutant IDH.

Clinical features of supratentorial cortical ependymomas: a report of 8 cases at a single center

Yuji Matsumoto¹, Tomotsugu Ichikawa^{1,2}, Kazuhiko Kurozumi¹, Yasuhiko Hattori¹, Yusuke Tomita¹, Toshihiko Shimizu¹, Yoshihiro Otani^{1,3}, Kentaro Fujii¹, Hiroyuki Yanai⁴, Isao Date¹

¹ Department of Neurological Surgery, Okayama University Graduate School of Medicine, Okayama, Japan,

² Department of Neurosurgery, Kagawa Prefectural Central Hospital, Kagawa, Japan,

³ Department of Neurosurgery, University of Texas Health Science Center at Houston, Houston, Texas, USA,

⁴ Department of Pathology, Okayama University Hospital, Okayama, Japan

【Objective】 Supratentorial cortical ependymomas (CEs) are rare. These lesions, selectively occurring in the superficial cortex, are not fully characterized. We herein summarize our experience with CEs.

【Methods】 The study population comprised 8 patients from our institution from January 1980 to April 2018. We retrospectively reviewed their clinical characteristics, imaging findings, treatment methods, pathological features, and clinical outcomes.

【Results】 The median age at diagnosis was 7.5 years. The 2 most common clinical manifestations were intracranial hypertension (n=3, 38%) and seizures (n=3, 38%). The tumors were located in the frontal lobe (n=4, 50%), parietal lobe (n=4, 50%). The mean tumor diameter was 70 mm. All tumors had a cystic appearance, and calcification was observed in 6 cases (75%). All patients underwent surgical resection. Gross total resection was achieved in 6 cases (75%), and subtotal resection was performed in 2 cases (25%). Seven tumors (88%) qualified as WHO grade III, and 1 tumor (12%) qualified as WHO grade II. Six tumors (75%) showed immunopositivity for L1CAM. Postoperative radiotherapy was performed for all patients with grade III tumors except children aged <3 years. Although 4 patients (50%) developed recurrence after the initial treatment, all were alive throughout the follow-up period.

【Conclusions】 Although most CEs are grade III and positive for L1CAM, which is a poor prognostic marker in supratentorial ependymomas, all patients showed a good prognosis. Gross total resection and adjuvant radiotherapy contribute to a relatively favorable prognosis of CEs compared with other supratentorial ependymomas.

The neuropathology of motor subtypes of Parkinson's disease: from the brainstem to basal ganglia

Bension S Tilley¹, Marc H Goldfinger¹, Ronald KB Pearce², Steve M Gentleman¹

¹Neuropathology Unit, Division of Brain Sciences, Department of Medicine, Imperial College London,

²Charing Cross Hospital, Imperial College Healthcare NHS Trust

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disorder with two main motor presentations: tremor-dominant (TD) and akinetic-rigid (AR). Previous studies of the neuropathology of subtypes have focused on the substantia nigra (SN) and locus coeruleus (LC), finding more degeneration in AR cases. However, these studies used H&E sections that do not allow for accurate demarcation of the SN from neighbouring pigmented nuclei. We have created a novel midbrain atlas using immunohistochemistry that accurately isolates the SN. SN neurons modulate the activity of striatal cholinergic interneurons (ChIs) which are dysregulated in PD and there is evidence of differential cholinergic tone in motor subtypes. **Methods:** 40 TD and 40 AR-presenting cases were selected from the Parkinson's UK Tissue Bank. Sectuibs from the midbrain and pons were immunostained for tyrosine-hydroxylase, α -synuclein, tau, amyloid- β and choline-acetyltransferase (ChAT) for basal ganglia sections. Based on our midbrain atlas, TH-neuron counts in the SN and LC were performed and ChI arborisation assessed in the striatum. Pathology was quantified using a %-coverage methodology. **Results:** There were no significant differences between PD motor subtypes in SN or LC TH-neuron counts. There was significantly more LC α -synuclein pathology in AR cases compared to TD. A reduction in primary and secondary arborisation was seen in striatal ChIs of AR cases compared to TD. **Conclusions:** We have shown, in contrast to previous studies, that motor subtypes are likely to be non-monoaminergic in their origins, perhaps reflecting differences in cholinergic tone in the striatum and other brain regions.

The accumulation of tyrosine hydroxylase to Lewy bodies in PLA2G6 associated neurodegeneration

Hisae Sumi-Akamaru^{1,2}, Yasuo Miki³, Yuichi Riku^{4,5,6}, Shinsuke Kato⁷, Koichi Wakabayashi³, Mari Yoshida⁵, Hideki Mochizuki²

¹ Department of Clinical Laboratory, Higashi-Osaka Medical Center,

² Department of Neurology, Graduate School of Medicine, Osaka University,

³ Department of Neuropathology, Institute of Brain Science, Hirosaki University Graduate School of Medicine,

⁴ Department of Neurology, Nagoya University Graduate School of Medicine,

⁵ Institute for Medical Science of Aging, Aichi Medical University,

⁶ Laboratoire de Neuropathologie, Groupe Hospitalier PITIE-SALPETRIERE,

⁷ Division of Neuropathology, Department of Brain and Neurosciences, Tottori University Faculty of Medicine

Introduction: Tyrosine hydroxylase (TH), a rate-limiting enzyme of catecholamine synthesis, binds to phospholipid membranes, like α -synuclein (α Syn). Recently, we reported that α Syn accumulates to the degenerated mitochondria both in the disease models and the patient with PLA2G6 dysfunction, in which the phospholipid metabolism is abnormal. To clarify the mechanism of α Syn accumulation in PLA2G6 associated neurodegeneration (PLAN), we analyzed the expression of TH in Lewy bodies. **Methods:** The expression of TH was quantitatively estimated in nigral neurons of PLAN (n=2, age 20, 48; duration 17, 23years) and sporadic Parkinson disease (sPD, n=7, average age 77; average duration 14). In the double immunohistochemistry against TH and phosphorylated α Syn, the colocalization rate was calculated in the Lewy bodies or pre-inclusions. **Results:** In PLAN, the TH expression in the neuronal cytoplasm was well preserved. The expression of TH was observed also on the surface of Lewy bodies and pre-inclusions, similarly to the localization of the mitochondrial marker protein. The rate of the colocalization was 90% and 83% in the neuronal inclusions of each PLAN case, respectively. In sPD, the expression of TH was observed diffusely in the halo of Lewy bodies. The colocalization was 27% of the total neuronal inclusions including Lewy bodies and pre-inclusions. **Conclusions:** The high expression of TH in Lewy bodies would be associated with the preserved expression of TH in the neurons of PLAN. The accumulation of TH on the surface of Lewy bodies might suggest that TH binds to the phospholipid membranes.

A new MSA model mice recapitulate some pathological and clinical features in human patients

Kunikazu Tanji¹, Yasuo Miki¹, Fumiaki Mori^{1,2}, Yoshikazu Nikaido², Hidemi Narita^{1,3}, Akiyoshi Kakita⁴, Hitoshi Tkahashi⁵, Koichi Wakabayashi¹

¹ Department of Neuropathology, Hirosaki University School of Medicine,

² Department of Anesthesiology, Hirosaki University School of Medicine,

³ Department of Rehabilitation Science, Hirosaki University of Health and Welf,

⁴ Department of Pathology Neuroscience, Brain Research Institute, University of Niigata,

⁵ Department of Pathology, Brain Research Institute, University of Niigata

[Introduction] Multiple system atrophy (MSA) is an adult-onset neurodegenerative disorder characterized clinically characterized by autonomic failure in addition to various combinations of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. Despite extensive research, the mechanism underlying disease progression in MSA remains unknown. Animal models of human diseases that recapitulate clinical, biochemical and pathological features are indispensable for understanding molecular mechanisms and advancing preclinical studies. However, model animals for MSA have been limited so far. Importantly, considering that MSA is an adult-onset disease, it would be more suitable that model animals manifest abnormal protein aggregates from adulthood. [Objective] To examine pathophysiological mechanism underlying MSA progression, we generated MSA model mice using Cre-loxp technique to express inducible alpha-synuclein, which is a major component of pathological hallmarks of MSA. [Results] From adulthood, our MSA mice showed that excessive alpha-synuclein expression in oligodendrocytes, resulted in abnormal alpha-synuclein accumulation and modifications similar to human MSA pathology. Also MSA mice exhibited a part of MSA-clinical features such as lower motor activity and sudden death. [Conclusion] These findings suggest that new MSA model mice would be useful to analyze the pathophysiological alteration underlying its disease progression.

Radiological, immunological, and pathological analysis of ependymal cells in neuromyelitis spectrum disorders

Fumihiro Yanagimura¹, Etsuji Saji¹, Takahiro Wakasugi¹, Yasuko Toyoshima², Akiyoshi Kakita², Hitoshi Takahashi², Osamu Onodera¹, Izumi Kawachi¹

¹Department of Neurology, Brain Research Institute, Niigata University,

²Department of Pathology, Brain Research Institute, Niigata University

OBJECTIVE: Neuromyelitis optica spectrum disorders (NMOSD) is a central nervous system inflammatory autoimmune disease with aquaporin-4 (AQP4) antibody as a disease-specific marker. On magnetic resonance images (MRI), although multiple sclerosis (MS) is characterized by a lesion perpendicular to the ventricular wall called Dawson's finger, NMOSD is characterized by a lesion along the ventricular wall called 'pencil-thin' ependymal enhancement. The details of radiological, immunological, and pathological features of the ependymal cells in NMOSD remain elusive. The objective of this study is to clarify characteristic features on the ependymal cells in NMOSD. **METHODS:** We retrospectively analyzed clinical, immunological and radiological features of 31 cases with NMOSD and 49 cases with MS. We then performed immunohistological examination (AQP4, Iba-1, activated complement C9neo, CD3, CD20) using other autopsied specimens of NMOSD (15 blocks) and disease control (6 blocks). **RESULTS:** On brain MRI, 'pencil-thin' ependymal enhancement was observed in NMOSD (1/31, 3%), but not in MS (0/49, 0%). AQP4 immunoreactivity was extensively disappeared on the ependymal cells (12/15, 80%) in NMOSD, while it was not observed in disease control (0/6, 0%). Furthermore, in the subependymal lesions of NMOSD, activated complement deposition with vasocentric patterns, granulocytes including neutrophils and eosinophils and activated microglia infiltration were observed. **Conclusion:** The 'pencil-thin' ependymal enhancement observed on brain MRI was a unique, but rare finding in NMOSD. The ependymal lesions in NMOSD were considered as 'AQP4-pathy' with complement-dependent cytotoxicity, similar to white matter lesions with loss of AQP4 immunoreactivity on astrocytes in the spinal cord and optic nerves of NMOSD.

The classification and clinical significances of autoantibodies against astrocytes

Lei Liu¹, Yueshan Piao², Jiawei Wang^{1,3}

¹ Department of Neurology, Beijing Tongren Hospital, Capital Medical University,

² Department of Pathology, Xuanwu Hospital, Capital Medical University,

³ Medical Research Center, Beijing Tongren Hospital, Capital Medical University

Introduction: Astrocytes make up of over 40% of all the cells in the CNS and perform a wide variety of functions. The discoveries of autoantibodies against astrocytic AQP4, GFAP and SOX1 have enriched the contents of neuroimmunology.(break)

Methods: In vitro indirect immunofluorescence assay.(break)

Results: We discriminate antibodies against three types of antigens: 1) membranous antigen, AQP4; 2) cytoplasmic antigen, GFAP; 3) nuclear antigen, SOX1. This characterization has direct implications for diagnostic workup, treatment and outcome. AQP4-IgG helps to differentiate neuromyelitis optica from multiple sclerosis and form spectrum diseases sharing with it. AQP4-IgG from patient's serum reacted with rat leptomeninges and vessel wall of brain parenchyma in linear pattern. It also reacted with parenchyma and vessel wall of primate optic nerve in fine linear pattern. GFAP-IgG is clinically associated with meningoencephalomyelitis. In rat hippocampus, GFAP-IgG from patient's CSF reacted with the cytoplasm and processes of astrocytes. In primate cerebellum, it reacted with the radial processes of Bergmann glia in the Purkinje cell layer and penetrated the whole molecular layer. SOX1-IgG is a newly identified paraneoplastic neurological syndrome antibodies. There is intense labeling of the nuclei of rat Bergmann glia with a patient's serum containing SOX1-IgG. Nuclei of small cell lung cancer cells of the same patient also immunoreacted with commercial SOX1 antibodies.(break)

Conclusion: AQP4-IgG has been proved to damage astrocytes and caused astrocytopathy. The potential pathophysiological mechanisms of GFAP-IgG and SOX1-IgG remain to be explored.

Neuronal surface antibody mediated autoimmune encephalitis and its paraneoplastic linkage

Lei Liu¹, Yueshan Piao², Jiawei Wang^{1,3}

¹ Department of Neurology, Beijing Tongren Hospital, Capital Medical University,

² Department of Pathology, Xuanwu Hospital, Capital Medical University,

³ Medical Research Center, Beijing Tongren Hospital, Capital Medical University

Introduction: Autoimmune encephalitis (AE) belongs to post infectious or noninfectious encephalitis and has ignited great enthusiasm around the world. But not until the discovery of anti-NMDA receptor antibody did neurologists notice the differences between antibodies against neuronal surface and nuclei.(break)

Methods: Three case reports and review of the literatures. Patients' sera and CSF were evaluated by indirect immunofluorescence assay on prefixed rat hippocampus and cerebellum. Not only the neuropil staining patterns of different antibodies were compared, but the resected ovarian teratoma, thymoma and small cell lung cancer were analyzed to identify potential auto-antigens.(break)

Results: According to different immunopathological mechanisms, AE could be roughly divided into forms with cellular and humoral immunity predominant. In terms of tumor associations, AE could be divided into paraneoplastic and non-paraneoplastic forms. In general, most paraneoplastic AE are cellular immunity predominant with CD8 positive cytotoxic T cells targeting the cell nuclear or cytoplasmic antigens. These T cells infiltrate brain tissue and cause irreversible damages. On the contrary, non-paraneoplastic AE are humoral immunity predominant with B cells producing antibodies against cell surface antigens. These antibodies, mostly IgG block cell surface amino acid receptors, ionic channels or cell-adhesion proteins and cause reversible changes by responding to immunotherapies. But there is always an exception to the general rule.(break)

Conclusion: By presenting three cases with occult neoplasm identified and resected, we proved disorders caused by antibodies against neuronal surface antigens, such as NMDA receptor, LGI1, CASPR2 and GABA receptor type B could also be paraneoplastic by nature.

DOCK8 regulates microglial activity in neuroinflammation

Kazuhiko Namekata¹, Xiaoli Guo¹, Atsuko Kimura¹, Nobutaka Arai², Chikako Harada¹, Takayuki Harada¹

¹ Visual Research Project, Tokyo Metropolitan Institute of Medical Science,

² Brain Pathology Research Center, Tokyo Metropolitan Institute of Medical Science

Introduction: Deducator of cytokinesis 8 (DOCK8) is a guanine nucleotide exchange factor. In humans, loss-of-function mutations in this gene are responsible for a combined immunodeficiency. In this study, we investigated the role of DOCK8 in microglia using two disease models: experimental autoimmune encephalomyelitis (EAE) for multiple sclerosis (MS), and optic nerve injury (ONI) for glaucoma. Also, we report a novel method for reconstructing 3D images of microglia to examine microglial dynamics.

Methods: A novel mouse line with DOCK8 deletion (DOCK8^{-/-}) was generated. EAE was induced with the myelin oligodendrocyte glycoprotein (MOG)₃₅₋₅₅ peptide. For obtaining 3D images of microglia, the retina, optic nerve or a section of the spinal cord were cleared and immunostained with an iba-1 antibody.

Results: We show that DOCK8 is expressed in microglia and its expression is increased in the MS patient brain and in mouse EAE. Clinical symptoms of DOCK8^{-/-} EAE mice were ameliorated and the number of iba-1 labelled microglia was reduced in the spinal cord and optic nerve of DOCK8^{-/-} EAE mice. Similarly, ONI-induced activation of microglia is suppressed in the DOCK8^{-/-} mouse retina. Furthermore, we demonstrate that DOCK8 deficiency hinders microglial migration and phagocytosis.

Conclusion: DOCK8 is expressed in microglia and DOCK8 deficiency suppresses microglial activity during neuroinflammation. DOCK8 may be a therapeutic target for diseases such as MS and glaucoma. Our novel method for visualizing microglia in 3D images will be a useful tool for studying cellular dynamics.

Pathological characteristics and anti-acid staining of non-tuberculous brain infection

Jing Gao^{1,2}, Chenhui Mao^{1,2}, Hang Shen², Jing Yuan², Qiwen Yang³, Yi Guo⁴, Liangrui Zhou⁵, Feng Feng⁶, Fang Li⁷, Bin Peng²

¹Neurological Department Neuropathological Lab Peking Union Medical College Hospital,

²Neurological Department Peking Union Medical College Hospital,

³Department of Clinical Laboratory Peking Union Medical College Hospital,

⁴Neurosurgical Department Peking Union Medical College Hospital,

⁵Pathological Department Peking Union Medical College Hospital,

⁶MTI Centre Peking Union Medical College Hospital, ⁷PET Centre Peking Union Medical College Hospital

Introduction: acid-fast staining can detect Mycobacterium, actinomycetes, Legionella micdadei; some cell inclusion. We report 6 brain biopsy cases with subacute multiple intracranial infection related with acid-fast staining. **Methods:** for HE slides with inflammation, 100X microscope observation must be done. When the neutrophils were found, the Gram staining, acid-fast staining and modified acid-fast stain were the first choice, then PAS, silver staining, CD3, CD20, CD68 are carried out. close cooperate with microbiologist and genetic analysis. **Results:** 6 cases were male 3, female 3, age 22-44. All biopsy has neutrophils. 5 cases were diagnosed as non-tuberculosis infection, followed up for years: 2 McMahan cocci, 2 nocardiosis and 1 atypical mycobacterium. Two cases were misdiagnosed as TB for acid-fast stain positive. Three cases were misdiagnosed as inflammatory demyelination. 4 cases of suspected pathogens were found under 100X microscope, 3 of them with gram / acid-fast / modified acid-fast staining positive, and 1 with negative staining were confirmed as atypical mycobacterium by the culture and genetic analysis.. There were 1 TB cases without pathogen under microscope, confirmed by culture. There was no significant difference between T and B cells. All the patients have no typical multinucleated giant cells. Creutzfeldt cell can be seen. **Conclusion:** neutrophils in brain biopsy are an important sign of infection. The acid-fast staining should be combined with GAM, modified acid-fast stain and PAS for diagnosis differentiation. 100X is very important for the microscopic observation of brain infection. Inflammation and demyelination are also common in infectious diseases.

Invasive aspergillosis of paranasal sinuses with orbitocranial and brain extensive extension

Erick Gomez-Apo¹, Alejandro Bonilla-Mendez¹, Mario Gamez-Rosales¹, Eric Mendoza-Oviedo¹, Marisol Vaca-Segura¹, Teresa Del-Angel-Arenas¹, Myrna Arrecillas-Zamora¹, Rogelio Trevino-Rangel², Alexandro Bonifaz¹, Laura Chavez-Macias¹

¹ General Hospital of Mexico, ² Department of Microbiology, School of Medicine, Uanl

BACKGROUND. Chronic invasive fungal sinusitis is a rare subtype of mycotic diseases. It is characterized by a slow onset. Usually occurs in immunocompromised patients and is almost always lethal without early treatment. **CLINIC CASE.** A forty-two-year-old man. He began four months before of death with headache, decreased view, increased volume of right orbit and nose, nasal secretion, anosmia and loss of 15 pounds in a month. He continued with bilateral amaurosis, absent bilateral pupillary reflexes, purulent ocular secretion and very marked exophthalmos. Diagnosis on RMN was esthesioneuroblastoma; biopsy was taken, the diagnosis was hyalohyphomycosis (fungus ball); he was treated with Amphotericin and Voriconazole; he continued with deterioration and died. **AUTOPSY FINDINGS.** The findings of autopsy were extensive destruction of orbitofrontal skeleton, ethmoid and sphenoid paranasal sinuses, with green exudate in ventral surface of frontal lobes with extension and destruction of cerebral parenchyma with abscess formation. On biopsy and autopsy, there were mycotic structures with *Aspergillus* features. On mycologic study, it was identified not-pigmented fungus with very slowly-growing in culture media. Molecular study was realized with final diagnosis of *Aspergillus nidulans* / *Emericella nidulans* infection. **CONCLUSION.** Rhinonasal disease with intracranial extension is the commonest pattern of *Aspergillus* infection followed by intracranial mass lesions. Craniocerebral aspergillosis in immunocompetent hosts has three patterns of presentation that seem to correlate with clinical outcomes. Intracerebral aspergillosis is associated with the worst clinical outcome. Patients with orbital and cranial base aspergillosis had good recovery.

Leprosy and Buruli ulcer - mycobacterial diseases with painless skin lesions

Masamichi Goto¹, Junichiro En²

¹National Sanatorium Hoshizuka-Keiaien, Kagoshima, Japan,

²International University of Health and Welfare, Chiba, Japan

Introduction: Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. *M. leprae* injures peripheral nerves and cause multiple mononeuropathy. Buruli ulcer is also a mycobacterial disease caused by *M. ulcerans*. Deep skin ulcers are formed, but curiously the ulcers are usually painless, that may lead to diagnostic delay. We compared the peripheral nerve pathology of these diseases.

Methods: Human skin biopsy specimens of leprosy and Buruli ulcer, footpads of *M. leprae*-inoculated nude mice, footpads of *M. ulcerans*-inoculated BALB/c mice were histologically evaluated. *M. ulcerans* produces toxic lipid mycolactone, thus footpads of mycolactone-injected BALB/c mice and Schwann cell lines exposed to mycolactone were also evaluated.

Results: In the nerves of early skin lesions of human lepromatous leprosy, unmyelinated Schwann cells were the main host cells of *M. leprae*, and in nude mice model *M. leprae* were observed mainly in macrophages. In *M. ulcerans*-inoculated mice, the bacilli invaded perineurium with vacuolar change of myelin sheaths. Von-Frey sensory test showed diminished pain response [Goto, *Am J Pathol* 2006]. Mycolactone-injected mice also showed similar findings [En, *Infect Immun* 2008]. Finally, mycolactone showed higher toxicity to cultured Schwann cells (SW10) than that to fibroblasts (L929) and macrophages (J774) [En, *PLOS Negl Trop Dis* 2017].

Conclusion: In leprosy, *M. leprae* selectively invaded Schwann cells and macrophages, but in Buruli ulcer, *M. ulcerans* did not show such specific tropism. As mycolactone showed high toxicity to Schwann cells, mycolactone is suggested to be responsible for the painless nature of Buruli ulcer.

Progression of neuropathology of Creutzfeldt-Jakob disease and its relation to clinical findings

Yasushi Iwasaki, Akio Akagi, Maya Mimuro, Hiroaki Miyahara, Mari Yoshida

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

Introduction: To improve understanding of Creutzfeldt-Jakob disease (CJD) through a clinicopathological investigation, we conducted an investigation of the clinical progression of CJD and its relation to cerebral cortical pathology. **Methods:** Forty-three cases of MM1-type sporadic CJD were included in the study. The average age at onset was 69.7 years, and the average disease duration was 13.5 months. **Results:** The earliest pathologic finding was spongiform change and the next was gliosis. Neuropil rarefaction subsequently appeared, followed by neuron loss. Based on these observations, we proposed the following stages of cerebral cortical pathology (stage I to VI): Stage I, spongiform change; Stage II, hypertrophic astrocytosis; Stage III, neuropil rarefaction; Stage IV, neuron loss; Stage V, status spongiosus; and Stage VI, large cavity formation. We found a statistically significant correlation between disease duration and stage. All diffusion-weighted brain magnetic resonance imaging-examined cases showed cortical hyperintensity at the time of first imaging (average of 1.6 months after onset). Myoclonus and periodic sharp-wave complexes were first observed on electroencephalograms at an average of 2.1 months and 2.2 months, respectively, after onset. The akinetic mutism state was observed 3.2 months after onset on average. **Conclusion:** The cortical hyperintensity seen on diffusion-weighted images is a better indicator of spongiform changes than of gliosis. The first observation times of cortical hyperintensity, myoclonus, and periodic sharp-wave complexes approximately correspond to the early phase of Stage II. The time to reach the akinetic mutism state approximately corresponds to the middle phase of Stage II.

Insights from biochemical analyses of regional distribution of Alzheimer's pathologies

Mitsuru Shinohara^{1,2}, Naoyuki Sato¹, Dennis W Dickson², Guojun Bu²

¹National Center for Geriatrics and Gerontology, Aichi, JAPAN, ²Mayo Clinic, Jacksonville, FL, USA

Introduction: Region-specific appearance of Alzheimer's pathologies, including A β and tau, has provided important clues to understand the disease pathogenesis. While region-wide analyses were mostly done by clinical imaging studies or postmortem microscopic studies, we performed biochemical analyses through introducing in-house ELISAs.

Methods: The amounts of A β , tau, apoE and other molecules related to A β metabolism or neurodegeneration were measured in twelve brain regions, including neocortical, limbic and subcortical areas from different stages of disease cases. We analyzed regional associations between these molecules together with difference in absolute amounts between groups.

Results: The regional distribution of full-length A β , which were liable to accumulate in neocortical areas, positively associated with synaptic markers, and negatively associated with soluble apoE and an astrocytic marker, suggesting the potential involvement of synapses, and apoE or astrocytes in A β accumulation (Shinohara et al., Acta Neuropathologica 2013). However, such associations were changed in familial Alzheimer's disease cases with mutations in *APP* or *PSEN1*, suggesting that different pathomechanism causes distinct regional A β accumulation (Shinohara et al., Brain 2014). N-terminally truncated A β 42, represented by pyroglutamylated A β 11-42, whose levels were increased in the symptomatic stage, were liable to accumulate in some limbic areas, and strongly associated with accumulation of tau and apoE, suggesting the critical roles of N-terminally truncated A β 42 in the disease progression (Shinohara et al., Brain 2017).

Conclusions: These results showed utility of our biochemical method analyzing the regional distribution of Alzheimer's pathologies to address the disease pathogenesis. Further studies are now underway and will be discussed.

The presence of A β toxic conformer in the inferior parietal cortex before A β plaque formation and its dynamic localization in aging

Yusuke Kageyama^{1,4}, Olga Pletnikova¹, Gay L Rudow¹, Ikuo Tooyama⁴, Kazuma Murakami⁵, Kazuhiro Irie⁵, Susan M Resnick⁶, David R Fowler⁷, Lee J Martin^{1,2}, Juan C Troncoso^{1,3}

¹Department of Pathology, The Johns Hopkins University School of Medicine,

²Department of Neuroscience, The Johns Hopkins University School of Medicine,

³Department of Neurology, The Johns Hopkins University School of Medicine,

⁴Molecular Neuroscience Research Center, Shiga University of Medical Science,

⁵Division of Food Science & Biotechnology, Graduate School of Agriculture, Kyoto University,

⁶Laboratory of Behavioral Neuroscience, NIH/NIA/IRP, ⁷Maryland Office of the Chief Medical Examiner

Introduction: Amyloid beta (A β) plays a critical role in the pathogenesis of amyloidopathies, notably Alzheimer's disease (AD). Solid-state NMR analysis has identified a particular A β conformation which forms oligomers and is neurotoxic. **Methods:** We used the 11A1 antibody that targets this toxic conformer, to examine its distribution with immunofluorescent staining in the postmortem parietal cortex of 35 human subjects, 30 to 65 years of age, found histologically free of AD lesions. **Results:** 11A1 immunoreactivity was found in cortical neurons, astrocytes, neuropil and perivascular spaces at 30 years of age. Approximately 85% of neurons and 75% of protoplasmic astrocytes showed 11A1 immunoreactivity, and those proportions of neurons and astrocytes remained stable with age. 11A1 immunoreactivity was identified in nearly 30% of perivascular spaces during the fourth and fifth decades. 11A1 immunoreactivity was present in the neuropil as 1-2 μ m particles. Imaging of neuropil 11A1 immunoreactive particle with vesicle markers showed colocalization limited to CD63, which was also detected in astrocytes but not in neurons. This finding suggests that astrocytes participate in the processing of the A β toxic conformer. Notably, in the sixth decade, at the same time that the proportion of perivascular spaces with 11A1 immunoreactivity declines to approximately 20%, the number of neuropil 11A1 immunoreactive particles sharply increased. **Conclusion:** The A β toxic conformer is present in various cell types and brain structure in the inferior parietal cortex. Around age 50 years, this steady state of A β changes with a decrease of perivascular A β and a concomitant increase in neuropil A β .

Sushi repeat-containing protein 1 co-accumulates with cerebrovascular A β deposits in cerebral amyloid angiopathy

Yasuteru Inoue¹, Mitsuharu Ueda¹, Masayoshi Tasaki¹, Akari Takeshima², Yohei Misumi¹, Takayuki Kosaka¹, Taro Yamashita¹, Hitoshi Takahashi², Akiyoshi Kakita², Yukio Ando¹

¹Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan,

²Department of Pathology, Brain Research Institute, Niigata University, Niigata, Japan

Introduction: Sporadic cerebral amyloid angiopathy (CAA) is characterized by cerebrovascular amyloid beta (A β) deposits and causes cerebral hemorrhage and dementia. Several molecules have reportedly co-accumulated with tissue amyloid deposits in patients with amyloidosis. The exact molecules that co-accumulate with cerebrovascular A β deposits are still not fully known. Here, to identify the key molecules in CAA diagnosis and pathogenesis that may lead to therapy for CAA, we used laser capture microdissection to perform proteomic analyses with cerebral blood vessels. **Methods:** We performed proteomic analyses with microdissected leptomeningeal arteries and cerebral neocortical arterioles from 8 cases with severe CAA, 12 cases with mild CAA, and 10 control cases without CAA, and determined the levels of highly expressed proteins in cerebral blood vessels in CAA. **Results:** We focused on sushi repeat-containing protein 1 (SRPX1), which is specifically expressed in CAA-affected cerebral blood vessels. Immunohistochemical studies revealed that SRPX1 co-accumulated with A β deposits in cerebral blood vessels of all autopsied cases with severe CAA. In contrast, no SRPX1 co-accumulated with A β deposits in senile plaques. Furthermore, we demonstrated that both A β 40 and A β 42 bound to SRPX1 in vitro and enhanced SRPX1 expression in primary cultures of cerebrovascular smooth muscle cells. SRPX1 enhanced caspase activity induced by A β 40. Knockdown of SRPX1, in contrast, reduced the formation of A β 40 accumulations and the activity of caspase in cultured cerebrovascular smooth muscle cells. **Conclusion:** SRPX1 may be a novel molecule that is up-regulated in cerebrovascular A β deposits and that may increase A β -induced cerebrovascular degeneration in CAA.

Sex and age interact to determine clinicopathologic differences in Alzheimer's disease

Amanda M. Liesinger¹, Neill R. Graff-Radford², Ranjan Duara³, Kelly M. Hinkle¹, Fadi S. Hanna Al-Shaikh¹, Sarah K. DiLello¹, McKenna F. Johnson¹, Dennis W. Dickson¹, Melissa E. Murray¹

¹Neuroscience Department, Mayo Clinic, Jacksonville, FL,

²Neurology Department, Mayo Clinic, Jacksonville, FL,

³Wein Center for Alzheimer's Disease and Memory disorders, Mount Sinai Medical Center, Miami Beach, FL

Women reportedly make up two-thirds of Alzheimer's disease (AD) dementia sufferers. Many estimates regarding AD, however, are based on clinical series lacking autopsy confirmation. The Florida Autopsied Multi-Ethnic (FLAME) cohort was queried for AD cases with a total of 1625 identified ranging in age from 53-102 years at death. Standard neuropathologic procedures were employed and clinical information was retrospectively collected. Clinicopathologic and genetic data were stratified by sex. Within the neuropathologically diagnosed AD cohort, the overall number of women and men did not differ. Men were younger at age onset, had a shorter disease duration, and more often had atypical (non-amnesic) clinical presentations. The frequency of autopsy-confirmed AD among women and men stratified by age at death revealed an inverse U-shaped curve in men and a U-shaped curve in women, with both curves having inflections at approximately 70 years of age. Regional densities of neurofibrillary tangles differed in women and men, especially when examined by age intervals. Women had overall greater severity of tangle density compared to men, especially in the hippocampus. Men and women did not differ in frequency of MAPT haplotype or APOE genotype. Atypical clinical presentations, younger age onset and shorter disease duration were more frequent in men, suggesting that the lower reported frequency of AD in men may be due to more frequent atypical clinical presentations not recognized as AD. Our data suggest that neuropathologically confirmed AD has the same frequency in women and men, but their clinical presentations ages at onset tend to differ.

O17-1

Possible distinction of four repeat tau-positive lesions of Alzheimer's disease and progressive supranuclear palsy probed by four repeat-specific antibodies

Momoko Ebashi^{1,4}, Miho Uematsu¹, Ayako Nakamura¹, Yoshinori Ito², Katsuiku Hirokawa³, Satoshi Kamei⁴, Toshiki Uchihara¹

¹Laboratory of Structural Neuropathology, Tokyo Metropolitan Institute of Medical Science,

²Yokuhukai Hospital, ³Nitobe Memorial Nakano General Hospital,

⁴Division of Neurology, Department of Medicine, Nihon University School of Medicine

Introduction: Accumulation of abnormal tau protein is the pathological hallmark shared between Alzheimer's disease (AD) and progressive supranuclear palsy (PSP). Their distinction is based on the distribution of tau-positive neurons, associated cytopathology or tau isoforms. It is generally believed that 4 repeat (4R)-tau lesions in AD and PSP are not readily distinguishable. In this study, we tried to distinguish immunorepresentation of 4R-tau through comparison between two different antibodies toward 4R-tau. *Methods:* Thirteen autopsied brains (4 AD, 4 PSP and 5 AD+PSP) were enrolled in this study. 4R-tau immunoreactivity probed either by polyclonal anti 4R-tau® or monoclonal RD4® was compared in each case, and evaluated the structural characteristic of 4R-tau. *Result:* The anti 4R-tau® labeled a larger number of AD-neurofibrillary tangles (NFTs) more intensely than RD4®. This difference was evident in AD-prone areas such as hippocampus and locus ceruleus (LC) that of RD4®, which is particularly highlighted in the hippocampus and LC in all 13 cases. In contrast, RD4® labeled a larger number of tuft-shaped astrocytes (TAs) more intensely than anti 4R-tau®. This preferential immunoreactivity of RD4® on TA over anti 4R-tau® was evident in PSP-prone regions such as the precentral gyrus and brainstem tegmentum even if AD and PSP pathologies are coexistent, while NFT in PSP cases exhibited equivalent immunoreactivity to anti 4R-tau® and RD4®. *Conclusion:* Preferential RD4® immunoreactivity on TA/PSP is in contrast with complementary preference of anti 4R-tau® on NFT/AD. This may provide a clue to clarify difference in molecular species of 4R-tau between AD and PSP.

TDP-43 pathology contributes to clinicopathological heterogeneity of corticobasal degeneration

Shunsuke Koga¹, Kouri Naomi², Ronald L. Walton¹, Keith A. Josephs³, Neill Graff-Radford⁴, Ryan J. Uitti⁴, Jay A. van Gerpen⁴, Zbigniew K. Wszolek⁴, Owen A. Ross¹, Dennis W. Dickson¹

¹ Department of Neuroscience, Mayo Clinic, ² Department of Pathology, Boston Children's Hospital,

³ Department of Neurology (Behavioural Neurology & Movement Disorders),

⁴ Department of Neurology, Mayo Clinic

Introduction: Corticobasal degeneration (CBD) is a clinicopathologically heterogeneous tauopathy, which has overlapping clinicopathologic and genetic characteristics with progressive supranuclear palsy (PSP). This study aimed to examine whether transactive response DNA-binding protein of 43 kDa (TDP-43) pathology contributes to clinicopathologic heterogeneity of CBD. **Methods:** Paraffin-embedded sections of the midbrain, pons, subthalamic nucleus, and basal forebrain from 187 autopsy-confirmed CBD cases were screened with immunohistochemistry for phospho-TDP-43. In cases having TDP-43 pathology, additional brain regions were immunostained. Hierarchical clustering analysis was performed based on the topographical distribution and severity of TDP-43 pathology, and clinicopathologic and genetic features were compared between the clusters. **Results:** TDP-43 pathology was observed in 45% of CBD cases, most frequently in the midbrain tegmentum (80% of TDP-43-positive cases), followed by the subthalamic nucleus (69%). TDP-43-positive CBD was divided into TDP-limited (52%) and TDP-severe (48%) groups by hierarchical clustering analysis. TDP-severe patients were more likely clinically diagnosed with PSP than TDP-limited and TDP-negative patients because of high frequency of downgaze palsy. Multivariable logistic regression model revealed that TDP-43 pathology in the midbrain tectum was strongly associated with the downgaze palsy. In addition, tau burden in olivopontocerebellar structures was significantly greater in TDP-43-positive than TDP-43-negative CBD cases. Genetic analyses revealed that MAPT H1/H1 genotype frequency was significantly lower in TDP-severe (65%) than in TDP-negative (89%) and TDP-limited (91%) CBD cases. **Conclusion:** TDP-severe CBD is a distinct clinicopathologic subtype of CBD, which presents with PSP-like presentations. Severe tau pathology in olivopontocerebellar structures may associate with this subtype.

Morphological features of neuronal and glial tau pathology in GGT (Types II and III)

Hidetomo Tanaka¹, Yasuko Toyoshima¹, Shinobu Kawakatsu², Takeshi Miura^{3,4}, Takeshi Ikeuchi³, Osamu Onodera⁴, Hitoshi Takahashi¹, Akiyoshi Kakita¹

¹ Department of Pathology, Brain Research Institute, Niigata University,

² Department of Neuropsychiatry, Aizu Medical Center, Fukushima Medical University,

³ Department of Molecular Genetics, Brain Research Institute, Niigata University,

⁴ Department of Neurology, Brain Research Institute, Niigata University

Introduction: Globular glial tauopathy (GGT) is a new 4-repeat tauopathy characterized pathologically by globular glial inclusions (GGIs), namely those affecting oligodendrocytes (GOIs) and astrocytes (GAIs). GGT is classified into three pathological subtypes (Types I, II and III), but the morphological features of the individual subtypes have not been investigated in detail. We have previously reported unique neuronal cytoplasmic inclusions (NCIs) in GGT Type III, but the morphological features of these NCIs are not included in the GGT consensus recommendations (Ahmed et al., 2013). Here, we investigated the morphological differences between the GGT subtypes, focusing on NCIs and GAIs. **Methods:** We investigated the tau pathology in 5 cases of GGT (Type II, n = 2; Type III, n = 3) in terms of the immunohistochemistry, biochemistry, 3D structure, ultrastructure, and quantity of the tau-positive inclusions. **Results:** GAIs in Type II were large with radiating process-like structures, whereas those in Type III were small with perikaryal large globular structures. 3D morphometric analysis supported the above findings. NCIs showed three unique subgroups in terms of shape: 1) diffusely granular, 2) thick and cord-like, and 3) round and horseshoe-shaped. Thick cord-like NCIs were a feature in both types. Interestingly, the round/horseshoe-shaped NCIs were observed only in Type III. **Conclusions:** The present findings suggest that morphological differences among GAIs may be a new feature to support classification of the subtypes, and that the presence of characteristic NCIs is a new common feature of GGT.

Sequential distribution patterns of aging-related tau astrogliopathy (ARTAG) in the human brain

Gabor G. Kovacs^{1,2}, Sharon X. Xie³, John L. Robinson², Edward B. Lee², Douglas H. Smith⁴, Theresa Schuck², Virginia M.-Y. Lee², John Q. Trojanowski²

¹Institute of Neurology, Medical University of Vienna, Vienna, Austria,

²Center for Neurodegenerative Disease Research (CNDR), Institute on Aging and Department of Pathology & Laboratory Medicine,

³Department of Biostatistics and Epidemiology,

⁴Department of Neurosurgery, Center for Brain Injury and Repair, the Perelman School of Medicine (PSOM) at the University of Pennsylvania, Philadelphia, PA, USA

Introduction: Aging-related tau astrogliopathy (ARTAG) describes tau pathology in astrocytes in different locations and anatomical regions. In the present study we addressed the question of whether sequential distribution patterns can be recognized for ARTAG.

Methods: By evaluating 687 postmortem brains with diverse disorders we identified ARTAG in 455. We evaluated frequencies and hierarchical clustering of anatomical involvement and used mathematical and statistical approaches to model the sequential distribution of ARTAG and astroglial tau pathologies across different brain regions.

Results: For subpial and white matter ARTAG we recognize three and two patterns, respectively, each with two stages initiated or ending in the amygdala. Subependymal ARTAG does not show a clear sequential pattern. For grey matter (GM) ARTAG we recognize a striatal pathway of spreading bidirectionally towards the cortex and/or amygdala, or the brainstem and an amygdala pathway, which precedes the involvement of the striatum and proceeds bidirectional spread towards the cortex or the brainstem.

Conclusion: Tau-astrogliopathy type-specific sequential patterns require the consideration of complex relationships of various tau pathologies and therefore cannot be simplified as neuron-based staging systems alone.

Autopsy on home-cared patients with neurological disorders. Nitobe model to improve patient care, medical education and research

Toshiki Uchihara¹, Shuta Toru¹, Michio Yamane², Hiroshi Shintaku^{3,4}, Masanobu Kitagawa⁴, Katsuiku Hirokawa³, Tetsuya Irie²

¹Neurology, Nitobe Memorial Nakano General Hospital,

²Internal Medicine, Nitobe Memorial Nakano General Hospital,

³Pathology, Nitobe Memorial Nakano General Hospital, ⁴Pathology, Tokyo Medical and Dental University

Introduction: Decline in the rate and number of autopsy is accelerating in all countries. Cost-conscious management of patients further accelerates this decline. Because increasing number of patients are cared for outside of hospital such as home or institutions for chronic care, autopsy on these individuals deceased outside of hospital may counteract this decline. **Method:** Nitobe model to support autopsy on these patients was constructed based on financial supports by several private grants. This Nitobe model includes autopsy units (Nitobe Memorial Hospital and Tokyo Medical and Dental University Hospital) and a support center to afford the cost for autopsy (3,000 USD/autopsy) and transport of the deceased. **Results:** Among 31 patients autopsied in this project, 3 deceased at home and 28 deceased at hospital after 2.1 yr (mean) of home care. This cohort included 9 ALS, 8DLB, 4PSP, 3AD, 2MyD, MSA, CBD, pure autonomic failure, leukoencephalopathy and cerebral hemorrhage. Some of the home care physicians became interested in examining the autopsy samples by themselves and in presenting the data in CPC or even in this meeting. Some of the patients' family or even patients themselves gave consent for autopsy during life. **Conclusion:** Autopsy on the deceased at home is a feasible strategy that can improve the quality of care. Increasing the number of autopsy may strengthen the scientific basis for medical education and research. Public financial support is indispensable to expand this Nitobe model so that similar system is available all over Japan or in the world.

Introducing the Digital Brain Tumor Atlas (DBTA), a freely available repository for brain tumor whole slide scans

Thomas Roetzer^{1,2}, Anna-Christina Moser^{1,2}, Petra Mercea^{2,3}, Romana Prihoda^{2,3}, Baran Atli^{1,2}, Johannes A. Hainfellner^{1,2}, Bernhard Baumann⁴, Georg Langs⁵, Adelheid Woehrer^{1,2}

¹ Institute of Neurology, Medical University of Vienna, Vienna, Austria,

² Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria,

³ Department of Neurosurgery, Medical University of Vienna, Vienna, Austria,

⁴ Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria,

⁵ Computational Imaging Research Lab, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria

Introduction: Digital pathology is increasingly recognized as useful tool for precision diagnostics. Typical tasks include tissue segmentation, disease classification, and enhanced prognostic rating. Yet, the underlying machine learning algorithms depend on the availability of large, freely available datasets for training. However, there are only few whole slide image (WSI) repositories available online, and those do not cover all brain tumor types in sufficient quality and quantity. **Methods:** Herein, we introduce the Digital Brain Tumor Atlas, which will comprise all brain tumor entities according to the current WHO classification. Using MedUni Vienna's neurobiobank as resource, we are in the process of scanning a total of 10,000 expert-selected H&E slides in high resolution using a Hamamatsu NanoZoomer XR scanner. All slides will be published online together with basic clinical annotations. **Results:** So far, we have digitized roughly 2,500 WSI covering 100 different brain tumor types. In parallel, information on gender, location, and age has been collected for all cases. For a subset of 500 glioma cases, we have further manually segmented tumor, necrotic and hemorrhagic areas. **Conclusions:** We introduce the Digital Brain Tumor Atlas, a freely available online repository for H&E slide scans of all brain tumor entities. The atlas will fill a critical gap and prove valuable 1. for training machine learning algorithms for enhanced diagnostics 2. as a training tool for young neuropathologists, and 3. as an independent, external validation dataset for digital pathology projects.

Allied neurosurgical results World War I and II

John Hedley-Whyte

Harvard University

Introduction: In 1941 Major, later Sir Benjamin Rycroft was teaching me to read. I asked "Why do the eye cases come to you while the neurosurgical cases are flown to Oxford?" "Neurosurgery is harder than the eye business. They are flown with catheters draining their spinal fluid." "Why?" "So they do not burst their brains." "Who thought that up?" "Cushing in Boston. He trained all the head doctors: Cairns at Oxford, Ross at Barts."

Methods: Harvard, Yale, Oxford and U.S. Library of Congress Archives and other sources were examined.

Results: In World War I Allied mortality from head injury was reduced from 37% to 20% after King George V in 1915 gave Harvey Cushing de facto control. His pupil, Sir Hugh Cairns, halved it to 10% in WWII. His transport protocol remains a modern standard of care, but required 10,000 DC3s, C47s, Dakotas and UK and US Nurse Air Nightingales and 130 Air Landing Strips, newly constructed in Europe alone. The Allied World War I and II Medical and Surgical Services were under the control of Presidents Wilson and FD Roosevelt and Kings George V and VI.

Conclusion: Cushing's 3-volume biography of Sir William Osler won a Pulitzer Prize. The Cushings were married from the Regius and Lady Osler's Oxford home. Before the Cushings' honeymoon it was arranged that President Teddy Roosevelt would give the Romanes Lecture on June 7, 1910 at Oxford University. Friendly relations with Japan were espoused.

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In order to keep neuropathology succession, teaching stuffs of neuropathology should deal with neuroanatomy, clinical clerkship, and clinical office for outpatients, as well as neuropathology

Shinsuke Kato, Shinichiro Kitao, Masahiro Ii, Hiroshi Kohama, Kosuke Yonekura, Yuki Kaida, Norihisa Itaki, Junko Yasui, Kana Oda, Keiko Kato

Division of Neuropathology, Tottori University Faculty of Medicine

Introduction: Our Neuropathology Division has expanded the field of clinical and practical medicine dealing with patients in addition to basic medical sciences, since we founded a neuropathology clinical office for outpatients in Tottori University in 2013. **Methods:** With respect to the education of the basic medicine, we have succeeded for students to learn smoothly neuropathology by our lecturing neuroanatomy. Regarding the education of the clinical medicine, in order to bring up the sixth-year medical students to be the physicians who want to major in neuropathology in the future, we educate outpatient clinic as one part of clinical clerkship. Around 2-4 third-year students study neuropathology during one month as Laboratory Assignment System (LAS). **Results:** As for the neuroanatomy, we deliver 20 hour-Lecture, perform 12 hour-BrainCutting practice, and instruct 3 hour-Tissue Observation training. Referring the neuropathology, 13 hour-Lecture and 15 hour-Tissue Observation training are carried out. Concerning the clinical clerkship, we teach the autopsy and surgical neuropathology as a routine. When we conduct an outpatient clinic, we make clinical-clerkship students attend the clinic with patients and physicians, and have them learn pathologic findings. Synchronously, we make these students understand that the patients are able to receive pathology services of high quality through the clinic. As excellent results of LAS, one student published English paper and one student passed USMLE Step1. **Conclusion:** In order to keep the succession to neuropathology in Medical University, it is necessary that neuropathologists deal with neuroanatomy, neuropathology, clinical clerkship, and outpatient clinic as high-quality diagnostic services.