Neuronal loss and progression of Alzheimer’s disease related pathology observed in a Swedish patient with clinical diagnosis of idiopathic normal pressure hydrocephalus

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\textit{Introduction:} Here we assessed changes observed in neuronal population, inflammation and hallmark lesions of Alzheimer’s disease (AD) occurring during 21 months, in one subject with AD and idiopathic normal pressure hydrocephalus (iNPH). \textit{Clinical summary:} 63 years old woman debuted with cognitive impairment in 2005. Two years later she was clinically diagnosed with AD and iNPH. Her symptoms progressed rapidly and liquor dynamics test led to ventriculoperitoneal shunt insertion. Cortical biopsy was taken during the shunt operation in 2010. She improved postoperatively in motor function and alertness. The patient passed away 21 months after shunt-surgery and a neuropathological assessment of the brain was performed. \textit{Pathological findings:} The cortical biopsy and the post-mortem brain displayed AD pathology. Morphometrically assessed immunoreactivity showed increase in hyperphosphorylated \( \tau \) (HP\( \tau \)) and amyloid-\( \beta \) (A\( \beta \))40 paralleled with decrease of A\( \beta \)42, neuronal markers (synaptophysin, microtubule associated protein 2, non-phosphorylated neurofilament H, embryonic lethal abnormal visual system proteins 3/4 HuC/HuD) and microglial markers (CD68, Human Leucocytic Antigen DR, ionized calcium-binding adaptor molecule 1). Glial fibrillary acidic protein and total A\( \beta \) were stable. Around the shunt-channel minor tissue damage with reactive changes was seen. \textit{Conclusion:} In a patient with iNPH and end-stage AD, progression of HP\( \tau \) pathology, neuronal loss, decrease in expression of A\( \beta \)42 and microglial markers were observed. The tissue damage near the shunt-channel was negligible. Post mortem neuropathological evaluation of the brain of previously biopsied patients with iNPH is recommended.
Effects of systemic infection on the brain in the late stage of Alzheimer's disease

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Introduction: Clinical studies indicate that systemic infection/inflammation may contribute to and accelerate Alzheimer's disease (AD). Animal models suggest that this may be due to enhanced proinflammatory changes in the brain. Methods: Cerebral tissue from controls and AD patients who died with systemic infection (16Ctrl; 40AD) or without (24Ctrl; 28AD) was immunolabelled and quantified for Aβ, phosphorylated (p)tau and several neuroinflammatory proteins. In AD, synaptic proteins were assessed by ELISA, and inflammation/related proteins and mRNA were measured by Multiplex Assays and qPCR. Results: Systemic infection did not modify Aβ, ptau or the synaptic proteins. In AD with systemic infection, there was increased IL6 and decreased IL5, IL7, IL12/IL23p40, IL15, IL16 and IL17A, associated with elevated expression of immunosuppressive genes (CHI3L1 and IL4R). This was related with decreased CD16 (grey matter) and CD68 (white matter) antigen loads, and increased CD64 (white matter). In AD without systemic infection, CD68, CD64, CHI3L1, IL4R and CCR2 (grey matter) were increased, and CD32a (white matter) was decreased. Associations (p<0.001) were observed between grey and white matter Iba1 (motility) in the controls without systemic infection; CD68 (phagocytosis) and CCR2 (myeloid recruitment) in AD without systemic infection; and CD64 (immunoglobulins) in both cohorts but with systemic infection only. Conclusion: Our findings suggest that terminal systemic infections modify AD neuroinflammation, apparently by promoting an immunosuppressive environment in the brain. This highlights that microglia have a complex role in both promoting and responding to the neurodegeneration.
The pathological characteristics of neuronal Apolipoprotein E in normal aged controls and AD brains

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Introduction: APOEε4 risk allele is well known to be the genetic factor for late onset Alzheimer disease (AD). Previous studies have suggested that APOEε4 increases amyloid β accumulation in human brains. However, the role in tau pathology remains uncertain. Methods: We investigated the distribution of intraneuronal apoE in hippocampus and temporal/occipital neocortex of normal aged controls and compared the results to pathologically confirmed AD cases with several APOE genotypes. In addition, we examined the colocalization of apoE and neurofibrillary tangles (NFT) to find out the role of apoE in tau pathology. Results: In control cases, we observed consistent and widespread apoE intraneuronal staining in hippocampus, especially higher in CA1 region. They showed moderate staining in the cortices. AD brains displayed the milder immunoreactivity in hippocampus but lower in the cortices, compared to control cases. ApoE antibodies labels various stages of neurons, including neurons without NFT, pre-tangle, and ghost tangle. APOEε4 carriers demonstrate lower apoE in neurons than other AD groups. As for tau pathology, the ratio of apoE in NFTs decreased as ε4 allele copy number increases. Conclusions: We assume that apoE has a neuroprotective role in control brains and APOEε4 has an influence on acceleration of tau pathology in AD.
Deep phenotyping and multi-omics analysis of a homogeneous sample of familiar Alzheimer's disease brains

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Introduction: Familial Alzheimer's disease (FAD) is often considered as the optimal study model for this disease. FAD is characterized by early dementia onset and severe neuropathology. We have been following the largest cohort in the world suffering from FAD, comprising 1100 PS1E280A carriers. Despite their common background, PS1E280A patients present wide clinical variability. In this study we explore the association of clinical and pathological phenotypes with high-throughput data analysis. Methods: 23 PS1E280A postmortem brains were selected for biochemical and histological studies based on quality of the samples. Studies included A\textsubscript{4} and Tau pathology characterization, wide exome scan, RNA sequencing and LS/MS analysis. Patients were grouped according to clinical or pathological features and multivariate, principal component and clustering analyses were performed for genomic, transcriptomic and proteomic data. Results: We found association of clinical features, such as disease duration or age of onset of dementia, with specific pathological and biochemical profiles for Tau pathology, kinases and protein degradation networks. Furthermore, we have identified association between specific cognitive profiles and protein networks not directly linked to amyloid beta or Tau pathology. Conclusion: Even in a genetically uniform sample with a clear etiology for AD it is possible to identify other pathological processes and biological variants that have a direct effect in disease presentation. The application of deep phenotyping and multi-omics analysis in neurodegenerative diseases promises to be a valid approach for identifying other biological processes that could act as disease modifiers and will assist in the design of better targeted therapies.
Supranuclear ophthalmoplegia, neck dorsiflexion, and midbrain tegmentum atrophy associated with brainstem pathology of Alzheimer's disease in Japan

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Introduction: It has been well known that Alzheimer's disease affect brainstem, however, clinical manifestation caused by brainstem involvement have not been elucidated. We encountered 2 cases presented supranuclear ophthalmoplegia, neck dorsiflexion, and midbrain tegmentum atrophy associated with barinstem pathology of Alzheimer's disease.

Clinical summary: Case 1 A 75-year-old man developed 9 years course of l-dopa nonresponsive parkinsonism, supranuclear ophthalmoplegia, and neck dorsiflexion at the terminal stage. MRI revealed atrophy of the midbrain tegmentum. Case 2 An 85-year-old man developed 9 years course of l-dopa responsive parkinsonism and subsequent dementia, followed by supranuclear ophthalmoplegia, neck dorsiflexion, and dementia. MRI revealed midbrain tegmentum and medial temporal lobe atrophy.

Pathological findings: Case 1 Cortical atrophy was moderate in frontal and temporal lobes. the substantia nigra and locus coeruleus were depigmented. Abundant senile plaques were detected in cerebral cortex (Braak C) and frequently detected in colliculi. Neurofibrillary tangles were positive for both 3R and 4R tau with the predominance of 3R tau. They were abundant in cerebral cortex (Braak VI), and frequent in colliculi. Lewy bodies were abundant in amygdala. Case 2 Substantia nigra showed thin but depigmentation was mild. Locus coeruleus showed depigmentation. Microscopic findings demonstrated pure Alzheimer's disease (tangle pathology: Braak V, plaque pathology: Braak C) with 3R dominant neurofibrillary tangles in substantia nigra, near riMLF, and superior colliculus. Senile plaques showed in superior colliculus. Neither Lewy body nor α-synuclein positive material were observed.

Conclusion: Alzheimer's pathology affect brainstem, which can cause supranuclear ophthalmoplegia, neck dorsiflexion, and atrophy of midbrain tegmentum.
Wnt signaling molecules are involved in the formation of rimmed vacuoles and granulovacuolar degeneration bodies

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Introduction: Previously, we have demonstrated that rimmed vacuoles (RVs) and granulovacuolar degeneration (GVD) bodies are immunopositive for a set of common molecules suggesting that both RVs and GVD bodies originate from similar structures on the plasma membrane of muscle cells and neuronal cells, i.e. the neuromuscular junction (NMJ) and the postsynaptic spine especially in terms of Wnt signaling pathway. Methods: We investigated the presence of components of NMJ in RVs and/or postsynaptic spine in GVD bodies immunohistochemically. The tested molecules are as follows; (1) dishevelled (Dvl) family proteins, (2) NMJ associated proteins (low density lipoprotein related protein 4:Lrp4, heat shock protein 70:Hsp70, βcatenin, phospho βcatenin, rapsyn, P21 activated kinase 1:PAK1, adenomatous polyposis coli;APC and ADP ribosylation factor 6;Arf6), (3) a lipid raft-associated molecule (phosphatidylinositol 4, 5 bisphosphate:PIP2), and (4) other proteins;prion, glycogen synthase kinase 3β:GSK3β. Results: In all cases of sporadic inclusion body myositis examined, RVs were immunopositive for Dvl3, Hsp70, βcatenin, PIP2, APC, prion and GSK3β. In all cases of Alzheimer disease examined, GVD bodies were immunopositive for Dvl3, phospho βcatenin, rapsyn, APC and PIP2. Conclusion: RVs and GVD bodies share common molecules associated with the Wnt signaling pathway, indicating that these structures share a common structural and functional origin.
Early tau pathology in young Japanese forensic autopsy series: Frequency and association with APOE genotype and suicidal risk

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Introduction: Early tau pathology of Alzheimer’s disease (ET) observed in brainstem such as locus ceruleus and raphe nuclei in young people are not known in detail. We aimed to reveal the demographic, genetic and clinical aspects of ET with Japanese forensic autopsies.

Methods: From a total of 1614 serial Japanese forensic autopsy cases, we detected the cases under 40 years of age. ET and senile plaques were assessed with Braak stages and Thal grade following immunohistochemistry. Genomic DNA was isolated from whole blood, and APOE was genotyped by Sanger sequencing.

Results: We assessed 187 cases (mean age 25.5±13.0 years, 125 males, 62 females, 0-39 years) and detected ET in 102 cases (54.5%, 13-39 years). ET was not related to sex and APOE genotype. Relatively high stage of ET (1a stage and over) cases showed significantly low suicide rate.

Conclusion: ET was high frequency in young Japanese, and had no relation to sex and APOE genotype. Tau pathology may not be a significant accelerating factor for suicide in the early pathological phase.
**Neuron-specific histone modification analysis of Alzheimer's disease brains**

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*Introduction:* To elucidate the pathomechanism of sporadic neurodegeneration, patients' brains are the most essential resources. However, they are vulnerable to postmortem degradation, that compromises precise analysis. Furthermore, they are composed of varieties of cells making difficult to extract neuron-specific information. To overcome these issues, we conducted neuronal histone modification analysis using fluorescent activated cell sorting (FACS) combined with chromatin immunoprecipitation (ChIP) and next-generation sequencing (NGS) to indirectly assess neuronal gene expression.

*Methods:* We examined the postmortem brain samples from eight sporadic AD patients and eight age-matched normal controls (NC). Neuronal nuclei were isolated from brain tissues using FACS and subjected to ChIP-Seq with anti-H3K4me3 antibody which is known to be bound to active promotor regions. The differentially bound regions between the two groups were searched using DiffBind.

*Results:* We detected two differentially bound regions (GENE A, B) between the two groups with false discovery rate (FDR) < 0.05. In GENE A, AD showed lower H3K4me3 methylation level of the transcription starting sites (TSS). In GENE B, AD showed higher H3K4me3 methylation level of the TSS. Indeed, immunostaining and western blotting consistently showed a significant reduction of protein A expression. Protein A is known to be associated with perineuronal nets formation.

*Conclusions:* We performed neuron-specific ChIP-seq and found a novel gene associated with sporadic AD. The result indicated usefulness of neuronal ChIP-Seq using postmortem brain when studying sporadic neurodegeneration.
A Japanese pedigree of Alzheimer's disease with novel presenilin 1 mutation Try215Arg and amyloid angiopathy. A report of three cases

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Introduction: Although 227 mutations in presenilin 1 (PSEN1) have been reported, clinicopathological study of several Alzheimer's disease (AD) cases in the same pedigree is limited. We described clinicopathological findings of 3 AD cases with PSEN1 Try215Arg mutation in the same family. Methods and Results: In this pedigree, 14 individuals over 4 generations were affected and three cases went to autopsy. The mean age of onset was 50 years and that of death was 61 years. Novel PSEN1 mutation Try215Arg was identified in 3 three cases. Patient 1 became amnestic at the age 46 years. Next 10 years, her dementia progressed and muscle rigidity was noted. She died at the age 60. The brain weighed 860g. Patient 2 became forgetful at the age 44 years. At 46 years, MMSE scored 16, and apraxia and visual agnosia were noted. MRI showed diffuse cortical atrophy and white matter hyperintensities. SPECT revealed parietal hypoperfusion. She died at the age 55. The brain weighed 860g. Patient 3 became forgetful and apathetic at the age 48 years. MRI at the age 56 showed diffuse cortical atrophy including hippocampus. CT scan at the age 59 revealed occipital and thalamic intracerebral hemorrhage. She died at the age 60. The brain weighed 790g. All three patients had amyloid angiopathy (AA) as well as abundant tangles and prominent amyloid depositions including cerebellum. There were no cotton wool plaques. Conclusion: AA was characteristics of PSEN1 Try215Arg mutation but the degree of AA displayed a variability in the same pedigree.
The first autopsy case of Alzheimer disease after treatment of anti-amyloid beta antibody (solanezumab)

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Introduction: We here report the first autopsy case of Alzheimer disease (AD) after treatment of solanezumab. Clinical summary: A sixty-year old man came to our clinic with complaint of forgetfulness. Neurological examination was unremarkable and MMSE was 21/30. MRI and FDG PET revealed cerebral atrophy and hypometabolism, consistent with AD. He participated double blind clinical trial of solanezumab for one and a half years and then open trial of active drug for three years. His decline of mental state did not ameliorate and at age 66, he admitted to our hospital for BPSD. Two weeks later, he died of aspiration pneumonia. The interval between the last administration of solanezumab and death was one month. Pathological findings: Neuropathologically, the brain weighed 1250 g. Gross examination was unremarkable. Histologically, Braak neurofibrillary tangle stage was 6, CERAD stage for senile plaque was C and Thal's amyloid stage was 5. Unique pathology of A beta included focal wiped out of senile plaques with preserved tangles in the left amygdala, in addition to multifocal moth-eaten-like disappearance of amyloid. Mild amyloid angiopathy was present. Conclusion: These pathological features mimic the result of active immunization of A beta. This case may indicate the effectiveness of passive immunotherapy to remove A beta but not tau from brains with AD.
Amyloid precursor protein plaque-like structures in late-onset Alzheimer disease

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Introduction: Amyloid-beta (Aβ) peptide, derived from the amyloid precursor protein (APP), has been viewed as a central contributor to Alzheimer Disease (AD) pathogenesis for many years. Many therapeutics have been developed that reduce Aβ load in patients but, to date, have all failed in clinical trials. To this end, we present a novel focus on APP as a pathological contributor in AD through investigation of various cases involving late-onset Alzheimer Disease (LOAD).

Clinical summary: 6 cases of LOAD were identified through neuropathological evaluation of Aβ and tau, age of onset, and reported family history. Generally cases had clinical signs of dementia; one case was included involving no history of dementia. Cases involving additional pathology (e.g. alpha-synuclein) were excluded.

Pathological findings: In addition to typical AD pathologic changes, interestingly, many of these cases demonstrate unique “plaque-like” and granular structures of APP that are separate from Aβ plaques. These structures appear extracellularly and bear resemblance to dystrophic neurites with no association to tau neurites (potentially preceding their development). We suggest that local accumulations of APP in plaque-like/neuritic-like aggregates, are involved in the pathogenesis of other AD changes, preceding tau, possibly contributing to tau dystrophic neurite formation.

Conclusion: Based on the neuropathologic observations of human AD cases, it is hypothesized that APP may play an active role in the development of other AD tau and beta amyloid pathology, beyond being just a passive player in the genesis of beta amyloid plaques.
**Distribution of different forms of Aβ in the brain of subjects with Alzheimer’s disease, MCI and intact cognition**

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**Introduction:** The diagnosis of AD dementia is based on clinical evaluation of the patient, but requires postmortem neuropathologic confirmation for definitive diagnosis. Advances in neuroimaging tools such as amyloid imaging radiotracers for PET scanning, raise the possibility of confirming the diagnosis of AD in the living patient. The clinical utilization of PET imaging has heightened the need for rigorous imaging-pathological correlations in AD in the brains of subjects in various cognitive states.

**Methods:** We performed immunostains for Aβ (6E10) and pyr-Aβ (pyrE3), and Thioflavin-S stains in cortical and subcortical structures of 28 subjects from the Baltimore Longitudinal Study of Aging, including AD, MCI, asymptomatic-AD, and controls.

**Results:** Total Aβ burden, compared between the AD and control groups, was significantly different for most brain regions. Aβ burden in AD subjects showed significant differences for the thalamus. Pyr-Aβ form displayed the same distribution of Aβ detected using 6E10 antibody; however, with more marked deposition in neocortical regions. Effect sizes for differences between AD and controls in the amount of Aβ plaques –measured with Thioflavin-S- were largest in entorhinal cortex, entorhinal-hippocampus cluster, and temporal-entorhinal-hippocampus cluster.

**Conclusion:** Our findings using Thioflavin-S as an Aβ marker showed distributions of pathology comparable to some neuroimaging studies using PET radioligands. Whereas the differences in Aβ deposition between AD and controls are marked with different methodologies and different forms of Aβ (i.e. the toxic form Pyr-Aβ), the differences are less conspicuous in early stages of the disease, which remain a challenge to both the neuropathologist and neuroimager.
Brain transcriptome analysis of Japanese population living in Brazil

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Environment impacts phenotype through epigenetic mechanisms. Comparison of individuals with similar genetic background living in different environmental conditions allows to unveil these mechanisms. We aim to identify targets under epigenetic regulation comparing transcriptome and methylome of brain samples from Japanese living in Japan and Brazil. Here, we present the first phase of this study of twelve Japanese Brazilian cases of the second generation of immigrants (age 47-95, mean 73.2yo). The neuropathological evaluation according to BBAR protocols classified 3 cases as Braak III Alzheimer Disease (AD), 3 cases as Argyrophilic Grain (AG), 3 cases as Lewy Body (LB), and 3 cases as normal (NC).

We performed RNASeq analysis of the amygdala of autopsy specimens to interrogate transcriptional changes associated with these conditions in the Illumina NextSeq. 600 genes were differentially expressed between the conditions and the controls. We used WebGestalt to interrogate biological processes overrepresented in these lists. In AD cases, immune system response (GOID:2376, \(p=3.62\times 10^{-8}\)) and regulation of cell proliferation (GOID:8284, \(p=2.67\times 10^{-6}\)) were among the processes most strongly enriched. Among the 65 genes with fold change >4 \(TACR3, TRAC, CSF3, SLC9A2, IL1B, SELE, IL6, ICAM1, IL32, SERPINA3, CXCL10, IFI44L, HAMP, HMOX1, OPN4, FCGR1B\) were relevantly connected in network of immune response. In AG cases, genes related to response to stress (GOID: 2952, \(p=1.31\times 10^{-5}\)) and aminoglycan catabolic process (GOID: 6026, \(p=0.0003\)) were observed. In LB cases, genes related to peptidyl-glutamine modification (GOID:18199, \(p=0.0002\)) and oxygen transport (GOID:15671, \(p=0.001\)) were detected. Methylome data will be integrated to these transcriptome data and the results compared to the dataset generated with Japanese-Japanese brain samples.
Cerebral hypoperfusion and Aβ interfere with pericyte trophic signalling pathways in Alzheimer's disease

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Introduction: Pericytes regulate multiple vascular functions. In AD precuneus we previously showed loss of pericytes, indicated by a reduction in the pericyte marker PDGFRB, correlating with markers of reduced oxygenation, and elevated Aβ. We have now explored possible mechanisms.

Methods: PDGFRB and markers of cerebral oxygenation (MAG:PLP1, VEGF) were measured as previously (Miners et al. J Cereb Blood Flow Metab 2018;38:103) in precuneus from 40 AD and 31 control brains. Human brain-derived pericytes were cultured in 2% oxygen for 72h ± Aβ40 or Aβ42. Pericyte trophic factors and receptors were measured by ELISA.

Results: PDGFRB level correlated positively with markers of better oxygenation (increased MAG:PLP1, decreased VEGF) in controls but not AD. Neither hypoxia nor exogenous Aβ (except at high levels) for 72h caused overt pericyte toxicity, but both reduced pericyte proliferation. Pericyte VEGF level rose in response to hypoxia, but so did VEGFR1 (anti-proliferative), and VEGFR2 and PDGFRB (both pro-proliferative) declined. Proliferation of pericytes in response to VEGF, PDGFBB or EDN1 was also inhibited by Aβ. Pericyte expression of Ang1 (pro-survival) was reduced by Aβ40 (100nM); that of Ang2 (pro-apoptotic) was elevated by hypoxia and by Aβ42 (100nM).

Conclusions: Hypoxia and Aβ interfere with trophic signalling pathways that regulate pericyte homeostasis. This is likely to block the proliferative response of pericytes to elevated VEGF, PDGFBB and EDN1 in AD, and to cause pericyte dysfunction and loss, as has been demonstrated in the disease. The mechanisms are unclear but may involve Aβ-mediated sequestration of trophic factors, or receptor inactivation.
P2-15

Zibotentan, an EDN1A antagonist, prevents Aβ-induced hypertension, maintains cerebral perfusion, and may have therapeutic potential for Alzheimer's disease

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Introduction: Cerebral blood flow is reduced in patients with Alzheimer's disease (AD). Aβ accumulation, a hallmark of AD, upregulates the cerebral endothelin system. We have investigated whether parenchymal infusion of Aβ40 modulates systemic blood pressure (BP), carotid blood flow and markers of cerebral hypoperfusion in Wistar rats, and also the effects of administering the endothelin-receptor antagonist zibotentan on Aβ-induced haemodynamic changes.

Methods: Normotensive 12-14wk male Wistar rats were assigned to one of four groups Aβ40-infused not on zibotentan (Aβ-zib); Aβ40-infused on zibotentan (Aβ+zib); saline-zib; and saline+zib. Aβ was infused into the striatum over 28d by mini-osmotic pump, blood pressure was monitored using an implanted radiotelemetry device, and carotid blood flow was measured by use of electromagnetic flow probes. After completion of the infusions, Aβ level and markers of tissue oxygenation were measured in the brain tissue.

Results: Infusion of Aβ induced a progressive rise in systemic BP. Zibotentan administration abrogated the effects of Aβ infusion on BP, without any adverse effect on carotid blood flow or cerebral oxygenation.

Conclusions: These findings provide further evidence that reduced cerebral perfusion caused by Aβ accumulation may induce mid-life hypertension. The amelioration of these effects by zibotentan raises the possibility that EDN receptor antagonists may have therapeutic potential in early AD.
Corticobasal syndrome-Pick's disease with Pick bodies: a clinicopathological study

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Introduction: Corticobasal syndrome (CBS) is characterized by an atypical parkinsonian syndrome with apraxia, and is associated with several distinct histopathologies, including corticobasal degeneration, other forms of tau-related degeneration such as progressive supranuclear palsy, and Alzheimer disease. However, Pick's disease (PiD), 3-repeat tauopathy, is rarely included in this clinical entity. We report the clinicopathological finding of a patient with CBS-PiD, which demonstrated the association between the presenting phenotype of CBS and the distribution of Pick bodies.

Clinical summary: A 80-year-old right-handed man gradually experienced increasing difficulty with speech and skill movement. He had speech of apraxia and right-limb apraxia with slight extrapyramidal signs, as well as end-stage dementia.

Pathological findings: Neuropathologically, focal cortical atrophy, neuronal loss, and gliosis were most prominent in the left opercular, precentral and postcentral gyri, and parietal lobes. Bodian's silver stain and 3-repeat tau immunohistochemistry showed numerous Pick bodies, which were diffusely present in those areas and, to a lesser degree, in the temporal lobes. By contrast, the degeneration in the subcortical gray matter was mild in the substantia nigra, subthalamic nucleus, globus pallidus, and striatum.

Conclusion: This case represents a rare histopathology of CBS, suggesting that the clinical features of PiD have a much wider spectrum than generally assumed. The clinical manifestations are thought to depend on the topographic distribution of Pick bodies, which located intensively to the frontoparietal region instead of the frontotemporal region.
Chronic traumatic encephalopathy and motor neuron disease in a retired football player

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Chronic traumatic encephalopathy (CTE) has been associated with clinical or neuropathologic features of amyotrophic lateral sclerosis. A 66 year-old former professional football player with a history of 30 concussions during his career was evaluated by a neurologist for weakness of the upper and lower extremities and mild memory loss. Nerve conduction studies showed fasciculations in the extremities and tongue. The clinical impression was motor neuron disease. At age 67, the patient died of respiratory failure. An autopsy was carried out. The brain, 1420 grams, was grossly unremarkable except for a small lacune in the left caudate nucleus and mild depigmentation in the substantia nigra. Histologic sections were stained with Luxol fast blue-H&E and antibodies to Abeta, ptau, alpha-synuclein, and pTDP43. The primary motor area showed mild loss of neurons in the lower cortical layers and neuronophagia. The spinal cord anterior horns contained neuronal loss and gliosis. The corticospinal tracts showed no myelin pallor. Tau-immunopositive inclusions were most numerous in neurons and glia in the entorhinal cortex, hippocampus, amygdala, and temporal neocortex. Multiple foci of ptau-positive glia were seen perivascularly and in the depths of sulci. Sparse tau-immunopositive inclusions were detected in the substantia nigra, locus coeruleus, and posterior medulla. pTDP43-immunopositive inclusions were seen in spinal cord neurons and glia. Frontal cortex contained sparse diffuse Abeta plaques. There was mild Abeta angiopathy. No alpha-synuclein aggregates were identified. The association of CTE with motor neuron disease raises etiologic questions about chronic traumatic head injury and neurodegeneration.
Aims: The human epidermal growth factor receptor family consists of 4 members that belong to the ErbB lineage of proteins (ErbB1-4). Neuregulin-1 (NRG1)/ErbB signaling regulates brain development, synaptic plasticity and neuronal survival. Change in ErbB4 expression levels have been implicated in the etiology or development of neurodegenerative diseases such as Alzheimers disease (AD), Parkinsons disease, and amyotrophic lateral sclerosis. So, we aimed at investigating whether the expression of NRG1 or ErbB proteins is altered in progressive supranuclear palsy (PSP) and AD. Methods: The brains of 10 PSP, 2 AD and 6 control patients were investigated by immunohistochemical and electron microscopy analysis. Results: Whereas C-terminal ErbB4 immunoreacitivity was partially but distinctly present in the cytoplasm and/or in the nucleus of neurons in control patients, it was rarely observed in the neuronal nuclei in PSP and AD patients. In contrast, neurofibrillary tangles in PSP and AD, coiled bodies and threads in PSP were robustly immunoreacive for C-terminal ErbB4. C-ErbB4 immunoreacitivity was expressed surrounding neuritic plaques in AD. Double immunofluorescence for C-terminal ErbB4 and phospho-tau revealed co-localization of these proteins within neuronal inclusions in PSP and AD and glial inclusions in PSP. To the contrary, there was no difference in the subcellular localization of NRG1, ErbB1, ErbB2, and N-terminal ErbB4 between control, PSP, and AD patients. These proteins were localized in the cytoplasm of neurons. Conclusions: Our present results suggest that decreased NRG1/ErbB4 signal transduction to the nucleus could be an important event in the pathogenesis of PSP and AD.
Glial three repeat tau accumulation in progressive supranuclear palsy

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Introduction: PSP is pathologically categorized as a 4-repeat tauopathy. Small amounts of pathological 3-repeat tau accumulation have been reported in neurons, whereas there are few reports about 3-repeat tau in glial cells. Clinical summary: A Japanese male complained unsteadiness in walking at age 71, and then frequently fell down the next year. He showed levodopa-unresponsive parkinsonian symptoms adding to supranuclear gaze palsy and frontal lobe dysfunction. He was in bedridden state at age 75. In advanced stage of disease, bilateral vocal cord paralysis, myoclonus, pyramidal signs, and ataxic respiration were observed. He died of aspiration pneumonia at age 84. Pathological findings: There was severe neuronal loss with gliosis in the brainstem tegmentum, substantia nigra, red nucleus, locus ceruleus, subthalamic nucleus, globus pallidus, dentate nucleus, and precentral cortex. Gallyas-Braak-positive and phosphorylated-tau-positive tufted astrocytes, coiled bodies, neurofibrillary tangles, and neuropil threads were seen in the above lesions. The neuropathologic criteria for PSP were clearly fulfilled. Notably, these structures were positive for 4-repeat tau, and many of them including tufted astrocytes were also positive for 3-repeat tau. Confocal imaging revealed 3-repeat tau immunoreactivity was superimposed on 4-repeat tau immunoreactivity in the neurofibrillary tangles and tufted astrocytes. Beta-amyloid deposits were only seen in hippocampus and putamen. Immunoblot analysis of sarkosyl-insoluble brain samples showed similar results to PSP. There was no MAPT mutation. Conclusion: Our case suggested that PSP patient, especially with long clinical course, would have the potential to develop 3-repeat tau accumulation in glial as well as neuronal cells.
Putaminal Tau Pathology in the Aging Japanese Population: The Hisayama Study

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Introduction: Hisayama study is a prospective cohort study commenced in 1961 in the town of Hisayama in Fukuoka Prefecture, Japan. In principle, all residents of the town of Hisayama are proposed to be autopsied when they die, and the total autopsy rate is about 75%. We previously reported that Alzheimer's disease (AD) and hippocampal tau deposits were increasing in recent years in Japan. In this study, we extend our observation towards putaminal tau pathology in the aging Japanese population.

Methods: We examined a series of autopsied cases from Hisayama residents obtained between 2009 and 2014 (224 cases). To evaluate tau pathology quantitatively, we performed immunohistochemistry with AT8 antibody and automated quantitative analysis using a platform called MATLAB.

Results: Tau deposits in putamen gradually increased around 70 years of age, and were correlated with the Braak stage. Certain AD cases showed severe tau deposits in putamen. Amyloid deposition in the putamen was not necessarily correlated with the putaminal tau deposition. We subdivided all cases into low CERAD (CERAD score 0-1) and high CERAD (CERAD score 2-3) groups to examine the effect of cerebral amyloid deposits on the putaminal tau pathology. The areal mean of putaminal tau deposition was significantly higher in the high CERAD group.

Conclusion: The cases with severe tau deposits in putamen were largely attributed to AD in the aging population.
Staging of brain lesions by phosphorylated tau-immunohistochemistry in the parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam

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Introduction: Parkinsonism-dementia complex (PDC) and amyotrophic lateral sclerosis (ALS) had been endemic neurodegenerative diseases in Guam of the western Pacific Ocean. Widespread occurrence of neurofibrillary tangles (NFTs), which are mainly composed of hyper phosphorylated tau, is the neuropathological hallmark of PDC, and relatively small amount of NFTs have been elucidated in patients with ALS and Guamanian non-PDC non-ALS control subjects. Methods: Immunohistochemistry for phosphorylated tau (AT8) was applied to six-micrometer-thick formalin-fixed paraffin-embedded sections of brains and spinal cords of thirteen Guamanian patients with PDC, nine ALS, five combined with PDC and ALS, and eight controls. The progression pattern and staging of the lesions with AT8-immunopositive were examined. Results: NFTs were positive for AT8 immunohistochemistry with rare neuropile threads, and four immunopositive stages were identified. Stage I: Macroscopically negative but a few AT8-positive NFTs in the temporal cortex or brain stem tegmentum. Stage II: Macroscopically positive slightly in the CA1 and transentorhinal cortex with or without patchy positivity in brainstem tegmentum. Stage III: slightly and diffusely immunopositive involving Ammon's horn, temporal cortex, superior and middle frontal cortex, neostriatum, amygdaloid nucleus, thalamus, hypothalamus, brainstem tegmentum, substantia nigra and pontine base. Stage IV: strongly immunopositive in every lesions of Stage III and inferior olivary nucleus, and slightly positive in the inferior frontal cortex and orbital cortex. Conclusion: Staging of brain lesions by phosphorylated tau-immunohistochemistry in the PDC, ALS and controls was identified four. Differences from Alzheimer's disease are rare neuropile threads and massive progression into brainstem.
Clinicopathological comparison between typical and non-typical progressive supranuclear palsy

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Introduction: Progressive supranuclear palsy (PSP) is one of the major tauopathies, characterized by the presence of tufted astrocytes and globose neurofibrillary tangles (NFT) showing four-repeat tau immunoreactivity. Clinically, PSP is classified into subtypes, including the PSP-Richardson syndrome (PSP-RS), which is considered as typical PSP, and PSP with predominant cerebellar ataxia (PSP-C). In this study, we examined the clinicopathological differences between PSP-RS and PSP-C.

Methods: Seven autopsy-confirmed PSP cases clinically considered as PSP-RS (6 cases) and as PSP-C (1 case) were examined. The degree of neurodegeneration, number of AT8-positive neurons, and degree of AT8-positive threads in several target areas were semi-quantitatively analyzed.

Results: Neurodegeneration was observed in the globus pallidus, subthalamus, and substantia nigra in all 7 cases. Immunohistochemical examination revealed that AT8-positive neurons and/or AT8-positive threads were widely present in all cases. In addition, the AT8 pathology of neurons/neuropil was a frequent feature not only in oculomotor nuclei, but also in the hypoglossal nuclei. In the PSP-C case, neurodegeneration with AT8 pathology was significant in the inferior olivary nuclei, pontine transverse fibers, pontine nuclei, and cerebellar white matter, compared to the PSP-RS cases.

Conclusion: We found that: 1) AT8 pathology severely affects the cerebellar afferent system of PSP-C, compared with that of PSP-RS, and 2) the AT8 pathology of neurons/neuropil was a frequent finding in the hypoglossal nuclei in PSP.
Anti-IgLON5 syndrome: a new entity at the crossroads of neurodegeneration and neuroimmunology

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**Introduction:** Since 2014, less than 30 patients have been described with a novel neurological syndrome characterized by parasomnia with sleep breathing disorder, accompanied by bulbar symptoms and specific IgG against the neuronal cell adhesion protein IgLON5. Autopsy showed neuronal loss, gliosis, extensive deposits of hyperphosphorylated tau, but absence of inflammatory infiltrates. The 3 and 4 repeat tau mainly involves hypothalamus and from tegmentum of the brainstem down to the upper cervical cord.

**Methods:** Case report and in vitro indirect immunofluorescence tissue based assay.

**Results:** A 59-year-old man was presented for admission after 6 months of parasomnia and 2 months of diplopia. His past medical history included dizziness and gait instability for two years. Brain MRI was unremarkable. Polysomnographic study showed frequent obstructive sleep apneic events with moderate oxyhemoglobin desaturations. Movement resembling manipulating objectives during sleep were also recorded. Laboratory evaluations only showed high titers of anti-IgLON5-IgG in both serum and CSF. He also carried specific HLA alleles, which are iconic in this syndrome. Immunoreactivity of patient's sample was a pattern of diffuse neural synaptic more intense in the cerebellum (granular layer more than molecular layer) than in the hippocampus.

**Conclusion** Although hyperphosphorylated repeat tau confine to certain area in autopsy study, anti-IgLON5-IgG reacts with the whole neuropil in vitro. This mismatch may lead to further investigations of pathophysiological mechanism and anatomical susceptibility of this syndrome.
Pathological validation study of corticobasal degeneration. An interim progress report of Japanese validation study of CBD (J-VAC study)

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Introduction

Corticobasal degeneration (CBD) is a sporadic neurodegenerative disorder characterized by progressive levodopa-nonresponsive rigidity with focal cortical signs, such as apraxia and aphasia, and often dementia of the frontal type. The expanding understanding of CBD indicate the wide range of clinicopathologic features. To elucidate these conditions, Japanese validation study of CBD (J-VAC study) group was established. The pathologic diagnosis is based on Office of Rare Diseases Neuropathologic Criteria for CBD proposed by Dickon et al. However, the identification of astrocytic inclusions sometimes revealed discordance among neuropathologists. Methods The aim is to standardize the pathologic diagnosis and elucidate the pitfalls of diagnostic process. The brains of Japanese 34 patients diagnosed pathologically as CBD from 12 institutes of J-VAC study group were reviewed by an independently group of neuropathologists. They reviewed the slides blinded to clinical information, and filled out a datasheet. Results The age at onset was 64.9 (mean) years. Disease duration was 8.1 years. CBS/CBD was the most frequent final clinical diagnosis (46%), followed by PSP (28%) and DAT (10%). The astrocytic inclusions were observed in both the Gallyas silver staining method and tau immunostains. The pathologic review has been currently in process, and the diagnostic inconsistence was found between the institutes. The discordance of the pathologic diagnosis might depend on difficulties of observation of astrocytic inclusions and staining methods, especially on the Gallyas silver stain. Conclusion We report an interim progress. It is important to validate of the pathologic diagnosis of rare disease CBD.
**P2-25**

**Globular glial tauopathy (GGT) presenting corticobasal syndrome**

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Introduction
GGT is a group of 4-repeat tauopathies presenting with motor neuron disease and/or frontotemporal dementia.

Clinical summary
A 72-year-old Japanese woman developed body weight loss of 14kg, clumsiness of the left hand and unsteadiness of gait and then progressively worsened. Neurologically, she showed limb-kinetic apraxia and pseudoathetosis of the left hand, and brisk tendon reflex on both sides with normal plantar reflex. Multiple lacunar infarcts were observed upon MR imaging. Dopamine transporter SPECT indicated decrease in the specific binding ratio bilaterally. She had a score on the Mini-Mental State Examination of 29/30, Raven's Colored Progressive Matrices of 24/36, Frontal Assessment Battery of 11/18 and trail making test of set B of 180 seconds. Subsequently, parkinsonism, frozen gait, cognitive impairment, disinhibition, motor aphasia, and ocular apraxia became apparent. At the age of 77, her extremities changed into flaccid paralysis and nasogastric feeding tube was needed. Her disease duration was 5 years.

Pathological findings
Her brain weight was 1110g. Cerebral atrophy was observed predominantly on precentral gyrus, superior parietal lobule with subcortical white matter and corticospinal tract degeneration. Globus pallidus, subthalamic nucleus, and substantia nigra showed mild to moderate neuronal loss and gliosis. Numerous 4R immunoreactive globular oligodendroglial inclusions, threads, were found in these regions. Several 4R immunoreactive astrocytic inclusions were different from typical tufted astrocytes and astrocytic plaques. Senile change were NFT Braak/AT8 stage III/III with argyrophilic grain stage I. These pathological findings were compatible to GGT.

Conclusion
CBS may develop in some cases with GGT.
Neuropathologic characteristics of patients with progressive supranuclear palsy who died within four years after the disease onset

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Introduction
Progressive supranuclear palsy (PSP) has been recognized as a tauopathy, and affected patients may manifest a wide variety of clinical symptoms. Practically, for patients with a short clinical course, a firm diagnosis of PSP may be difficult. Here we investigated the histopathological characteristics of autopsied patients with PSP who had died during the early stage.

Materials and Methods
From a total of 60 autopsy-proven patients with PSP, we retrieved four in whom PSP had been suspected clinically, but who had died unexpectedly within 4 years after onset. Multiple paraffin-embedded tissue sections throughout the brain were used for tau-immunohistochemistry with the AT8 antibody and the Gallyas-Braak silver method. Semi-quantitative evaluation was performed.

Results
The degeneration pattern appeared to be similar in all patients, with moderate neuronal loss in the substantia nigra, mild loss in the globus pallidus and subthalamus, and mild gliosis in the cerebellar dentate nucleus. Interestingly, the tau distribution pattern was distinct from neuronal degeneration, and the degree of tau accumulation differed among patients; the basal ganglia and subthalamus were the most prominent sites, and the cerebral cortex, cerebellar dentate nucleus and brainstem were also involved. In the motor cortex and basal ganglia, tau had accumulated mainly in glia, whereas in the brainstem it was deposited in neurons.

Conclusion
The initial symptoms of PSP may be associated with neuronal degeneration. Vulnerability of neurons and glia to tau deposition appears to differ among brain regions and individual patients, suggesting an association with symptomatic variability.
Clinicopathological characteristics of progressive supranuclear palsy manifesting cerebral cortical symptoms

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Introduction: There exists a wide clinical spectrum of progressive supranuclear palsy (PSP). The aim of the present study was to clarify the clinicopathological characteristics of Japanese patients with atypical PSP who exhibited cerebral cortical symptoms as an early and predominant feature.

Methods: We retrospectively reviewed the medical records of 59 patients with autopsy-proven PSP. By using core features employed in the latest diagnostic criteria (Mov Disord 2017), we selected patients that showed cerebral cortical dysfunction (C1-3) earlier than or within one year following the development of supranuclear gaze palsy (O1) and repeated falls (P1) (PSP-CC group). We also selected patients with usual PSP that manifested O1 and P1 without or preceding C1-3 features (PSP-RS group). We quantified tau load in various brain regions including cerebral cortical, subcortical, and brainstem areas, paying attention to the lesion laterality.

Results: Six and seven cases comprised PSP-CC and PSP-RS groups, respectively. In the PSP-CC group, a variety of cerebral cortical dysfunction, including speech disorder, bradyphrenia, disinhibition, and sensory deficit were observed. Tau load in the motor cortex and superior parietal lobule was significantly heavier in the PSP-CC group. In addition, 3 from PSP-CC group had a more severe cortical tau burden in the hemisphere ipsilateral to the side with predominant atrophy on brain MRI and decreased blood flow on SPECT.

Conclusions: Some patients with PSP manifest a variety of cerebral cortical dysfunction from early disease stage, likely as a result of severe and often asymmetrical cerebral cortical involvement.
An autopsied case of atypical tauopathy with globular glial inclusions

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Introduction: Globular glial tauopathy (GGT) is a group of tauopathies characterized by widespread globular glial inclusions (GGIs). GGT, however, exhibits a wide range of clinicopathological features, making its definition ambiguous. We describe an autopsied case of atypical tauopathy with unique clinical presentation and distribution pattern of GGIs.

Clinical Summary: A 62-year-old woman presented with tremor and dyscoordination in her left limbs. She initially responded to L-DOPA treatment, but further developed gait and cognitive disturbances. Her aunt displayed the similar symptoms. The imaging studies showed atrophy of the midbrain tegmentum and she was diagnosed to have progressive supranuclear palsy. Eventually, she became bedridden and died of aspiration pneumonia at the age of 79 after 17 years from her initial symptom.

Pathological findings: Postmortem examination revealed severe neurodegeneration with many phosphorylated-tau-positive neuronal as well as glial inclusions in the internal segment of the globus pallidum and subthalamic nuclei. The glial ones included globular oligodendrogial inclusions, coiled bodies and globular astrocytic inclusions. The latter rarely showed argyrophilic reactivity with Gallyas staining. These tau-positive inclusions were also scattered in the frontal lobe, tegmentum of the brainstem, substantia nigra, inferior olive and dentate nuclei of the cerebellum.

Conclusions: Although the findings suggest the diagnosis of "GGT, type 2", the clinical presentation, positive family history and distribution pattern of tau inclusions are not concordant with those of the type 2 reported. Further biochemical characterization of GGIs and molecular genetic analyses are to be necessary to establish more stringent criteria for GGT.
Pathologically suspected frontotemporal dementia and parkinsonism linked to chromosome 17: a case report in Japan

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Introduction: Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) is a major neurodegenerative syndrome characterised by behavioural and personality changes, cognitive decline, and motor symptoms. Case reports are limited on a sporadic case of the disorder. Clinical summary: A 68-year-old Japanese man visited our hospital because of clumsiness of the left hand. No tremor was noted, but rigidity and bradykinesia were observed in the left hand. There was no family history of neurodegenerative disorder. Idiopathic Parkinson's disease was initially diagnosed. Later, the motor symptom was slightly advanced and cognitive decline developed although behavioural and personality abnormalities were not observed. At age of 88 years, he was admitted to our hospital because of multiple cerebral infarct. After several episodes of pneumonia due to dysphagia, he died. Pathological findings: The substantia nigra was affected with predominantly left-sided neuronal loss and gliosis. Both 3- and 4-repeat taus were positive in neurons and astrocytes. Despite the presence of throne-shaped astrocytes, astrocyte tangles were almost absent. Staining with anti-amyloid beta peptides antibody showed classic and diffuse plaques only in the occipital lobe. Lewy bodies were observed in the left dorsal nucleus of vagus nerve, not in the substantia nigra or the locus ceruleus. Conclusion: Clinical and pathological findings are suggestive of a diagnosis of FTDP-17. Unfortunately, a definite diagnosis was not achieved because of insufficient sample volume available. Our case shows that FTDP-17 should be considered in patients with atypical parkinsonism and cognitive decline despite absence of personality changes and family history.
An autopsy case of incipient Pick's disease with long-standing history of schizophrenia

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Introduction: Neuropathology in the early stage of Pick disease remains poorly understood.

Clinical summary: The present report describes a 74-year-old female autopsy case of sudden arrhythmogenic death. Although she had a 37-year history of schizophrenia and had been medicated, she was not limited in activities of daily life. Pathological findings: Brain weight was 1,116 g. The only mild cerebral atrophy with dilatation of cerebral ventricle was found. Phosphorelated tau (AT8) and 3-repeat-tau positive Pick bodies (PBs) was found in the brain: These were relative frequent in inferior frontal, middle and inferior temporal, frontoorbital, ambient and cingulate gyrus, and was rarely in other gyrus of frontal and temporal lobe, limbic area. PBs in the neocortical region were more frequently found in ventral side and the upper (layer II) and lower (layer V and VI) layers. Moderate to large amount of AT8 positive neurofibrillary tangle and small amount of neuronal thread were found in limbic area and mid brain. Senile plaque and Lewy pathology was not found. Conclusion: Although we determined that Pick disease in present case was incipient and did not have correlation with Schizophrenia in alive, PBs and other tau pathology may synergistically contribute to getting lost the way her home. The lack of distinct sign indicating frontotemporal dementia could be associated with restricted extension of neocortical PBs and lack of neuronal loss. Neuropathological examination for forensic autopsy cases could provide a better understanding of the pathological appearance of preclinical Pick's disease.
Immunohistochemical detection of phosphorylated alpha-synuclein in the brain of a tauopathy model, rTg4510 mice

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Introduction: The accumulation of specific phosphorylated protein aggregates in the brain is a hallmark of neurodegenerative disorders. Specifically, hyperphosphorylated tau (hp-tau) accumulates in Alzheimer's disease, frontotemporal dementia with Parkinisonism linked to chromosome 17, and progressive supranuclear palsy; furthermore, phosphorylated alpha-synuclein (p-aSyn) accumulates in Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Moreover, co-deposition of different pathological protein aggregates is common in the brains of individuals with neurodegenerative diseases. Methods: We used rTg4510 mice that overexpress human P301L mutant tau, and FVB/N-C57BL/6J mice. The mice were euthanized at 3, 6, 8.5, and 10 months of age, and the brains were collected. We searched hp-tau and p-aSyn deposition in the brain of the mice by immunohistochemistry. Results: Human hp-tau and mouse p-aSyn aggregates were detected within the same neuronal cells mainly in the hippocampal CA1 area, entorhinal cortex and amygdala of rTg4510 mice and increased with age. Semi-quantitative analysis revealed a significant regional correlation between hp-tau and p-aSyn accumulation. Conclusion: The results indicate that endogenous mouse aSyn protein is phosphorylated and accumulates with hp-tau aggregation in neurons, and suggest that the overexpression of human P301L mutant tau may enhance endogenous aSyn phosphorylation and aggregation via a similar hyperphosphorylation mechanism in vivo. This synergic effect between tau and aSyn accumulation may exacerbate the pathology of several neurodegenerative disorders with co-occurrence of hp-tau and p-aSyn aggregation.
NODDING SYNDROME IN UGANDA: Histologic evidence for a novel frontotemporal degeneration tauopathy

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Nodding syndrome is an endemic neurologic disorder of unknown cause that affects children in the subsistence-farming communities of East Africa. We report the neuropathologic findings in 5 fatal cases (13-18 years of age at death) of nodding syndrome from the Acholi people in northern Uganda. Neuropathologic examination revealed tau-immunoreactive neuronal neurofibrillary tangles, pre-tangles, neuropil threads, and dot-like lesions involving the cerebral cortex, subcortical nuclei and brainstem. Occasional tufted astrocytes and plaque-like structures were also present. There was preferential involvement of the frontal and temporal lobes in a patchy distribution, mostly involving superficial cortical lamina. In severely involved areas of neocortex, there were tau-immunoreactive threads in subcortical white matter. The mesencephalopontine tegmental nuclei, substantia nigra, and locus coeruleus revealed globose neurofibrillary tangles and threads. The pathologic features of nodding syndrome shared characteristics with both corticobasal degeneration and progressive supranuclear palsy. We conclude that nodding syndrome is a newly recognized neurodegenerative disease in East Africa and may represent a novel variant of frontotemporal degeneration tauopathy.
Phosphorylated tau deposition in the spinal motor neurons in sporadic amyotrophic lateral sclerosis

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Less is known about tau accumulation in patients with amyotrophic lateral sclerosis (ALS). We investigated whether abnormal phosphorylated tau can accumulate in the spinal motor neurons in patients with ALS, and if any, which accumulation is predominantly composed of 3-repeat or 4-repeat phosphorylated tau. Eleven patients with ALS (7 men and 4 women) (mean age at death: 68.4 years) were enrolled in this study. With paraffin-embedded axial slice of the spinal cord at the level of cervical, thoracic, lumbar and sacral segments, immunohistochemistry was performed. All the patients had TDP-43-positive cytoplasmic inclusions in the spinal motor neurons. Although, the distribution of AT-8-positive lesions was very sparse, the tau-positive inclusions and neurites were detected in eight out of 11 patients with ALS. The cervical cord was the most frequently affected segment (five out of 11 patients (45.5%)), followed by thoracic (three patients (27.3%)) and lumbar (one patient (9.1%)). Tau pathology was not detected in the sacral segment. According to previous report, this prevalence of tau burden was almost equivalent to or less than that of normal aging spinal cord. The AT-8 lesions were positive for 3-repeat tau but negative for 4-repeat tau. Because the number of patients was very small in this study, the relationship between tau lesions, TDP-43 pathology and motor neuron sign could not be uncovered. Further study is needed to clarify whether TDP-43 pathology could have a potential to contribute to the presence of tau pathology, and whether tau pathology could increase the clinical severity of ALS.
Are Bunina bodies generated as a byproduct in the process of TDP-43 degradation?

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Introduction: Sporadic amyotrophic lateral sclerosis (sALS) is characterized pathologically by loss of motor neurons with occurrence of TDP-43-immunoreactive skein-like and round inclusions. Lewy body-like hyaline inclusions (LBHIs) are also found in a small proportion of sALS cases as well as in individuals with familial ALS with mutations of the Cu/Zn superoxide dismutase (SOD1) gene. LBHIs in sALS are immunopositive for TDP-43, but not for SOD1. The occurrence of Bunina bodies (BBs) is another pathological feature of sALS. BBs are immunonegative for TDP-43 but immunopositive for cystatin C, transferrin, peripherin and sortilin-related receptor CNS expressed 2 (SorCS2). Despite differences between BBs and TDP-43 inclusions in terms of protein constituents and ultrastructure, the two inclusions are known to be linked. Subject: We investigated a case of sALS of 10 months' duration in which many round inclusions, LBHIs and BBs were found in the anterior horn cells. Results: Our immunohistochemical and ultrastructural studies revealed the presence of BBs within the skein-like and round inclusions, and in the LBHIs. Co-localization of BB-related proteins (cystatin C, transferrin and SorCS2) and TDP-43 was also confirmed in the halo of LBHIs as well as in the marginal portion of the skein-like and round inclusions. Conclusion: These findings support the possibility that BBs may originate from TDP-43 inclusions. Considering that BB-related proteins are involved in the lysosomal and endosomal pathway, BBs might be generated as a byproduct in the process of TDP-43 degradation.
TDP-43 pathology in FTLD-subtypes

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Introduction: Following the discovery of 43-kDa TAR DNA-binding protein (TDP-43) as the ubiquitinated protein in most cases of FTLD-U, the harmonized classification of FTLD-TDP was agreed upon, which includes four subtypes, FTLD-TDP types A, B, C and D. Occasionally it is difficult to assign a case of FTLD-TDP to a specific pathologic subtype. Method: We formally re-evaluated the TDP-43-ir pathologic features that characterize the different FTLD-TDP subtypes to see if the current classification could be refined. Result: In our series of 91 cases, 95% were classified as one of the common FTLD-TDP subtype (35% A, 55% B, 10% C). The rest, 5%, did not easily fit into one specific FTLD-TDP sub-type. One case showed changes that were consistent with combined type B and type C pathology, one showed type B with NIIs, two showed type B or variant with some long, thin DNAs, and one showed type C variant with NIIs. Of the 91 FTLD-TDP cases, 20 had C9orf72 repeat expansions, which included 5 type A cases, 13 type B cases, the one combined type B and C case, and the one type B variant with NIIs case. Conclusion: These findings suggest that the pathologic criteria for subtyping FTLD cases based on TDP-43 immunohistochemistry (IHC) is useful. But up to 5% of FTLD-TDP cases may have combined or unclassifiable TDP pathology that does not appear to be consistently associated with C9 repeat expansion, and in our cohort, only a minority of cases with C9 repeat expansion have combined FTLD-TDP subtypes.
Immunohistochemical comparison of past and present patients with Kii amyotrophic lateral sclerosis

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Introduction: Kii amyotrophic lateral sclerosis (ALS) is characterized neuropathologically by widespread tau pathology including neurofibrillary tangles (NFT) and various glial inclusions, in addition to the classical ALS pathology. In recent years, the incidence of ALS has decreased in south Wakayama Prefecture, but it is not clear that environmental change is the cause. In this study, we investigated whether changes in the environment may have affected the pathological features of Kii ALS.

Methods: We examined brain tissue from 6 Kii ALS patients autopsied between 1965 and 1977, and from 3 Kii ALS patients who died between 2013 and 2016, respectively.

Results: All 9 patients showed similar topography of NFT distribution in the motor cortex, frontal lobe, temporal lobe, hippocampus, amygdala, and brainstem. NFTs were observed predominantly in the superficial layer of these cerebral cortices. In addition, in all patients, we detected granular hazy inclusions and granular or fuzzy tau immunoreactivity in processes of astrocytes as glial cytoplasmic inclusions. The distribution of TDP-43-positive neurocytoplasmic inclusions (NCI) was similar among the 9 patients, with immunoreactivity detected in the spinal cord and cerebral cortices. The cortical distribution patterns of TDP-43 pathology matched that of Type B of the Mackenzie's classification. Deposits of amyloid beta were either sparse or absent in all patients.

Conclusion: Our results suggest that the fundamental pathologic features of Kii ALS have not changed in patients over a range of years, in spite of changes in the environment.
Linear polyubiquitination occurs following K48-linked polyubiquitination in Alzheimer's disease

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Introduction: In patients with Alzheimer's disease (AD), various ubiquitinated pathologic structures are observed in the brain. During the ubiquitination of target proteins, several linkage forms of polyubiquitin chains are generated. Of these, the linear polyubiquitin (LUb) chain is believed to regulate NF-kB signaling. We examined the expression of LUb chains and compared it to the expression of K48-linked polyubiquitin (K48Ub) chains in AD-affected brains using immunohistochemical techniques.

Methods: Hippocampal and temporal lobe tissue from the postmortem brains of 6 neuropathologically-diagnosed patients with AD were analyzed. Paraffin-embedded hippocampal and temporal lobe sections were examined immunohistochemically using anti-LUb, anti-K48Ub, and anti-ubiquitin antibodies.

Results: Pathological structures such as dystrophic neurites of senile plaques, neurofibrillary tangles (NFT), neuropil threads, and granulovacuolar degeneration showed anti-LUb antibody immunoreactivity. Among these structures, neuropil threads were stained to a lesser extent by LUb than by K48Ub staining. The ratio of LUb-positive NFT to K48Ub-positive NFT was significantly lower in the temporal lobe (11%) than in the CA1 (47%) region.

Conclusion: Our results demonstrate that a subset of ubiquitin-positive pathological structures that appear in the AD-affected brain also show LUb immunoreactivity. In the region where NFT appear later, the accumulation of LUb is less than that of K48Ub. This suggests that linear polyubiquitination occurs following K48-linked polyubiquitination in the AD-affected brain. Moreover, the lower degree of LUb immunoreactivity in neuropil threads suggests that the occurrence of linear polyubiquitination depends on the size of the substrate.
Clinicopathologic features of two patients with sporadic amyotrophic lateral sclerosis who maintained communication ability for over 30 years

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Introduction: A small proportion of sporadic amyotrophic lateral sclerosis (SALS) patients are able to survive for a long period. We report the clinicopathologic features of two unrelated patients with SALS receiving tracheostomy and invasive ventilation (TIV) support who were able to maintain their communication ability for more than 30 years after disease onset.

Case histories:
Patient 1 was a 41-years-old woman who developed progressive muscle weakness. She introduced TIV at the age of 47 years. Her disease progressed extremely slowly, and she remained able to communicate via eye and mandibular movements until the end of her life. She died of liver failure at the age of 78 years.

Patient 2 was a 38-years-old man who developed bilateral lower limb weakness and spasm in the left lower limb. TIV was introduced at the age of 42 years. He was able to communicate via mandibular movements until the end of his life. He died of pulmonary alveolar proteinosis at the age of 69 years.

Pathological findings: The histopathological features of the CNS in patients 1 and 2 were quite similar. Neuronal loss was confined to the motor neuron system, and apparently mild in degree. As both patients showed phosphorylated TDP-43-immunoreactive neuronal cytoplasmic inclusions (NCIs) and glial cytoplasmic inclusions (GCIs) in the CNS, but the number of these inclusions was extremely small.

Discussion: There may be a distinct subgroup of patients with SALS, who can survive and maintain communication ability for an unusually long period, accompanied by very mild TDP-43 pathology.
A Japanese autopsy case of sporadic frontotemporal lobar degeneration with TAR-DNA binding protein 43-positive inclusions (FTLD-TDP) clinically diagnosed as corticobasal syndrome (CBS)

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Introduction: In many cases of FTLD-TDP, frontotemporal dementia or semantic dementia symptoms precede asymmetric motor disturbances. We present a sporadic autopsy case of FTLD-TDP in which motor disturbances preceded dementia symptoms, with a diagnosis of CBS. Clinical summary: The patient was a man aged 33 years at onset, and the duration was 15 years. He presented with dysarthria, spastic gait disturbance, rigidity, and hyperreflexia on the right dominant side. At 11 years after onset, he showed behavioral-variant frontotemporal dementia symptoms, such as hyperphagia, oral tendency, pica, and perseveration. Head magnetic resonance imaging revealed left hemi-brain severe atrophy. Dopamine transporter single-photon emission computed tomography with ioflupane showed specific binding ratio (SBR) decline on the left side. Thus, he was diagnosed with CBS. Pathological findings: His brain weighed 840 g. Neuron loss with gliosis was seen from the frontal lobe and precentral gyrus to the parietooccipital lobes and at the anterior horn cells of the cervical spinal cord. The substantia nigra showed extremely severe neuron loss. Pyramidal tract degeneration was dominant on the left side, with severe small fiber loss. Immunostaining for phosphorylated TDP-43 revealed short dystrophic neurites (DNs) and neuronal cytoplasmic and intranuclear inclusions in the cortex and basal ganglia. Although there were no Bunina bodies, skein-like inclusions, or round inclusions, a few DNs and glial cytoplasmic inclusions were seen in the lower motor neurons. Conclusion: The patient was pathologically diagnosed with FTLD-TDP. It is difficult to diagnose FTLD-TDP when asymmetrical motor impairments precede dementia.
An autopsy case of an elderly individual with incidentally diagnosed TDP-43 proteinopathy

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Introduction: Neuropathology in the early stage of frontotemporal lobar degeneration with TDP-43 proteinopathy remains poorly understood. Clinical summary: The present report describes a 77-year-old male autopsy case of sudden cardiac death due to senile cardiac amyloidosis. Although he had a 15-year history of hypertension and a 5-year history of atrial fibrillation, he did not exhibit clinical history suggesting neuropsychiatric disease. Pathological findings: Brain weight was 1,250 g. The atrophy was more severe in the anterior and basal side of the temporal pole. Restricted, but severe neuronal loss with neuronal cytoplasmic inclusions (NCIs) and dominant accumulation of TDP-43 in the temporal pole, as well as in the entorhinal cortex and amygdala. Neuronal loss in the orbitofrontal cortex was not evident with little accumulation of TDP-43. NCIs in the neocortical region were found in the upper layers (layer II and III) and lower layers (layer V and VI). A small number of dystrophic neurites (DNs) was also found in each area with an accumulation of TDP-43. TDP-43 accumulation was not found in the brain stem or spinal cord. Conclusion: We determined that TDP-43 pathology in the present case was not due to normal aging but may be significant pathological lesion. The lack of distinct clinical symptoms in the present case could be associated with restricted extension of neocortical TDP-43 pathology and neuronal loss. We believe that neuropathological examination for forensic autopsy cases could provide a better understanding of the clinical and pathological appearance of preclinical or very early stage of TDP-43 proteinopathy.
Distribution of phosphorylated TDP-43 and phosphorylated tau in the temporal lobe of patients with sporadic ALS who died within one year after clinical onset

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Introduction: We previously showed that amyotrophic lateral sclerosis (ALS) patients in the totally locked-in state (communication stage V) showed rapidly-progressing symptoms and common pathological lesions beyond motor neurons. Then we revealed that ALS patients who died within one year after onset showed phosphorylated TAR DNA-binding protein 43 (pTDP-43)-immunoreactive (ir) neuronal cytoplasmic inclusions (NCIs) similar to those of stage V patients. Furthermore, we investigate the temporal lobe of the patients that contain NCIs in dentate granule neurons corresponding to Nishihira’s ALS type2. Methods: We enrolled 6 patients who died within one year after clinical onset of sporadic ALS-TDP-43. We evaluated the degree of pTDP-43-ir and phosphorylated tau (AT8)-ir NCIs semi-quantitatively in the temporal tip, temporal cortex, hippocampal subiculum, and circular sulcus of insula. Results: In the temporal tip, we found more pTDP-43-ir than AT8-ir NCIs in 3 patients, fewer in 2 patients, and similar in 1 patient. In the hippocampal subiculum, AT8-ir NCIs were observed along the perforant path, whereas pTDP-43-ir NCIs were observed outside of the perforant path. In the circular sulcus of insula, we observed pTDP-43-ir NCIs in all 6 patients and AT8-ir NCIs in 5 patients, with the number of pTDP-43-ir NCIs exceeding that of AT8-ir NCIs. The temporal cortex contained the least NCIs. Braak NFT stage was I to III. Conclusion: The temporal lobe of ALS-TDP-43 patients even within one year after onset contained pTDP-43 and AT8-ir NCIs in the same area as patients with ALS-FTLD. The circular sulcus of insula was the affected area.
Morphological alterations of spinal motor neurons with dendritic and axonal TDP-43 accumulation in patients with ALS type 2b

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Introduction: ALS type 2b (ALS-2b) is a distinct subgroup of ALS-TDP characterized by accumulation of phosphorylated TDP-43 in dendritic spines and axon terminals. The prognosis of patients with ALS-2b is poor, despite relative preservation of lower motor neurons in comparison with other ALS-TDP subgroups. This study aimed to clarify the morphological alterations of spinal motor neurons in ALS-2b.

Methods: We examined the spinal L4 segment from 5 patients diagnosed pathologically as having ALS-2b and 3 controls. We performed immunohistochemistry and double-labeling immunofluorescence using antibodies against TDP-43, choline acetyltransferase (ChAT), and trans-Golgi network. ChAT-positive neurons in the anterior horns were regarded as motor neurons, and the frequency of both Golgi apparatus (GA) fragmentation and nuclear clearance of TDP-43 was evaluated.

Results: GA fragmentation and TDP-43 nuclear clearance were significantly more frequent in ALS-2b than in controls (GA: 91±8.4% and 13±13%, p<0.001, TDP-43: 85±10% and 37±15%, p<0.001, respectively). Almost all motor neurons with TDP-43 nuclear clearance showed GA fragmentation in ALS-2b, but such neurons were rarely seen in controls. Interestingly, the motor neurons with TDP-43 nuclear clearance in ALS-2b harbored no TDP-43-positive cytoplasmic inclusions, and moreover abundant dendritic and axonal accumulation of TDP-43 was evident.

Conclusion: In ALS-2b, motor neurons show distinct morphological alterations probably associated with dendritic and axonal accumulation of TDP-43, suggesting progressive dysfunction in the spinal motor neurons, and thus explaining the poor prognosis.
Autopsy-proven amyotrophic lateral sclerosis coexisted with Parkinson's disease: a novel association of TDP-43 proteinopathy and a-synucleinopathy (ALS/PD in Tokushima)

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Introduction: Coexistence of amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD) with Lewy bodies (LB) is reported to be rare, except for ALS/PD Complex in Guam or Kii Peninsula (ALS/PD Kii). Methods: We screened 320 patients with ALS registered to the Tokushima University Hospital in Shikoku Island, Japan. We extracted ALS patients who showed parkinsonism during their clinical courses and evaluated their neurological and neuroimaging findings. Results: The autopsy of three patients demonstrated ALS-TDP-43 complicated by PD with LB. On gross inspection, we observed depigmentation of the substantia nigra and locus ceruleus as well as atrophy of the spinal ventral roots in both patients. Microscopically, degeneration including neuronal loss with gliosis was observed in the substantia nigra, locus ceruleus, dorsal motor nucleus of the vagus, nucleus of the hypoglossal nerve, and ventral horn of the spinal cord. The involvement of upper motor neurons was confirmed by degeneration of the corticospinal tract and loss of Betz cells in the precentral gyrus. Bunina bodies were identified in lower motor neurons. Phosphorylated TDP-43-immunoreactive neuronal cytoplasmic skein or round inclusions and glial inclusions were observed in upper and lower motor neuron areas as well as in non-motor areas in one case. Lewy bodies immunoreactive for phosphorylated a-synuclein were abundant in the central and peripheral nervous systems. These cases lacked tau pathology and, thus, were distinct from ALS/PD Kii. Conclusions: Our investigation supports the possible establishment of a new disease entity and broadens the spectrum of proteinopathy in ALS and PD (ALS/PD in Tokushima).
An autopsy case of amyotrophic lateral sclerosis with a TARDBP N358S mutation

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We report the first autopsy case of a thirty-nine year old Japanese woman with a novel TARDBP N358S mutation, presenting with predominant upper motor signs. She experienced one-month history of dysarthria and gait difficulty. At her first visit to our clinic, she presented pseudobulbar type dysarthria and proximal dominant weakness accompanying hyperreflexia without muscle atrophy. Babinski sign was negative. Needle electoromyography detected resting potential in her limbs and trunks. Sequencing of the coding regions of the TARDBP disclosed a single base-pair change at position 1073 from A-to-G (A1073G) in exon 6 (N358S mutation) in this patient and her father. No mutation in SOD1 nor FUS was found. She became bedridden due to progressive weakness one month later and died of respiratory failure 99 days after the admission. Neuropathologically, there were severe degeneration of primary motor area and mild affection of spinal anterior horn. Immunohistochery with phosphorylated TDP43 demonstrated positive cytoplasmic round inclusions in the precentral cortex and anterior horn cells of the spinal cord. We studied the self-association of the wild type (wt) and N358S mutation by utilizing Thioflavin-S (ThS) binding assay. N358S mutation peptide showed significant fluorescence upon binding to ThS. Unlike the previously reported ALS cases with TARDBP mutation, our case presented prominent loss of upper motor neurons, commensurate with clinical signs. Further studies are needed to elucidate the pathological role of N358S mutation in TARDBP.
Amyotrophic lateral sclerosis-associated Ataxin-2 colocalized to ribosomal protein S6 in the human brain

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Introduction: There is a growing evidence indicating that Ataxin-2 (ATXN2) is important as a modifier of amyotrophic lateral sclerosis (ALS) and its potential therapeutic target. To understand the physiological role of ATXN2 and its involvement in ALS, we have investigated the localization of ATXN2 protein in the human brain.

Methods: We examined two normal human brain subjects, of which one was 4% paraformaldehyde-fixed, frozen floating sections, and the other was formalin-fixed, paraffin-embedded tissue sections. We performed a single immunoperoxidase labeling or a double immunofluorescence labeling using organelle specific antibodies, to analyze the anatomical or cellular distribution of ATXN2 protein. Colocalization of proteins were statistically analyzed according to the Pearson correlation coefficient and the Manders' overlap coefficient methods.

Results: The sensitivity of anti-ATXN2 immunoreactivity was higher in floating sections than in paraffin sections, indicating that anti-ATXN2 sensitivity was influenced by fixation methods. ATXN2 protein is observed in distinct neurons of the cerebral cortex, hippocampus, striatum and midbrain, and localizes to the neuronal perikarya predominantly, and to their proximal dendritic and axonal processes to a lesser extent. Double immunofluorescence labeling experiments revealed that of ATXN2 positive neurons, 70% of them were S6-positive and 50% were calnexin or LC3B positive.

Conclusion: The present study shows the highest rate of localization of ATXN2 in the ribosomes in neurons of the human brain. The results are consistent with the hypothesis that disruption of RNA metabolism involves in the pathogenesis of ALS.
What can neurophysiologists learn from neuropathology in diagnosis of amyotrophic lateral sclerosis (ALS)?

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Background: Clinical neurophysiological studies form a core in diagnosis of ALS. However, those cases without upper motor neuron (UMN) signs always cause problems. Method: We conducted internationally standard neurophysiological protocol for diagnosis of ALS and recruited suspected patients for brain donation. Four patients donated their bodies between 2015 and 2017. Three of them fitted into clinically probable or definite ALS and one lacked UMN signs. Neurological examinations, electromyography (EMG) and pathological findings of the last case were comparatively reviewed. Case reports: The patient was an 81 year-old man with progressive weakness of the right upper and lower limbs. Needle EMG revealed denervation potentials and chronic neurogenic changes but the EMG abnormality did not meet diagnostic criteria. UMN signs and dementia were not evident throughout the course. He died three years later. Neuropathological examination revealed severe loss of spinal anterior horn cells with Bunina bodies and TDP proteinopathy (Brettschneider Stage 2). Extensive examination of the primary motor area (PMA) detected a very few neuronophagia of Betz cells in contrast with other three cases. Discussion and Conclusion: Our series fulfilled pathological criteria of ALS but severity in the involvement of PMA was commensurate with clinical findings. The presented case did not have a chance for clinical trials and then more sensitive clinical method to detect involvement of UMN is required. In addition, this difference in severity of the involvement of UMN may represent different species of accumulated TDP-43 just like prion disease. Further correlative clinical, physiological and pathological studies are indicated.
P2-47

Upregulated expression of activated caspase-9 immunoreactivity in brains with alpha-synucleinopathy

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\textbf{Introduction:} The mitochondria play an important role in apoptotic cell death, and the released cytochrome c from the mitochondria promotes the formation of the apoptosome, which contains cytochrome c, Apaf-1 and caspase-9, resulting in the activation of caspase-9 and the promotion of the apoptotic cascade. The purpose of this study is to investigate the role of mitochondria-related apoptosis in patients with alpha-synucleinopathies.

\textbf{Methods:} Formalin-fixed, paraffin-embedded sections from 8 normal subjects, 10 patients with Parkinson disease (PD), 5 patients with dementia with Lewy bodies (DLB) and 10 patients with multiple system atrophy (MSA) were prepared. The deparaffinized sections were immunostained with primary antibodies against cytochrome c, Apaf-1, caspase-9 and activated caspase-9. Some sections were double-immunostained with activated caspase-9 and alpha-synuclein or glial markers.

\textbf{Results:} In the normal brains, various types of neurons were immunostained with cytochrome c, Apaf-1 and caspase-9, but no or faint activated caspase-9 immunoreactivity was observed. In the diseased brains, activated caspase-9 immunoreactivity was increased in both neuronal and glial elements, and 70-80\% of brainstem-type and cortical Lewy bodies (LBs), glial cytoplasmic inclusions (GCIs) and neuronal cytoplasmic inclusions (NCIs) were intensely immunoreactive for activated caspase-9. Brainstem-type and cortical LBs, GCIs and NCIs were also immunopositive for cytochrome c, Apaf-1 and caspase-9.

\textbf{Conclusion:} Our results suggest that the formation of the apoptosome accompanied by the activation of caspase-9 may occur in brains affected by PD, DLB and MSA, and that mitochondria-related apoptosis may be associated with the pathogenesis of alpha-synucleinopathies.
Four cases of multiple system atrophy with marked cortical atrophy and neuronal cytoplasmic inclusions in the temporal cortex

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Introduction: Multiple system atrophy (MSA) is a sporadic neurodegenerative disease, which manifests as a combination of dysautonomia, cerebellar dysfunction, and parkinsonism. Generally, the neocortex and limbic systems show less pathological changes in MSA. However, atypical MSA with frontotemporal lobe degeneration have been reported. We report four autopsy cases with marked cortical atrophy and neuronal cytoplasmic inclusions (NCIs) in the temporal cortex. Methods: We reviewed 159 consecutively autopsied Japanese patients with pathologically diagnosed MSA at our institute. Results: Four patients (2.5%; one male and three females; age at onset, 45, 41, 60, and 63 years, respectively) were diagnosed with atypical MSA with prominent temporal lobe degeneration. All the patients were clinically diagnosed with MSA in the premortem period (one MSA-C, three MSA-P). Memory impairment was observed in three cases, but none had features of frontotemporal dementia. The disease duration was 25, 15, 14, and 14 years, respectively. Pathologically, all the cases met the criteria for MSA, which included severe olivopontocerebellar degeneration and various striatonigral degenerations with glial cytoplasmic inclusions. All the cases showed temporal atrophy with limbic alpha-synuclein-positive NCI and neurites. Varying degrees of NCI were observed in the frontal cortex, basal ganglia, and brainstem. One case showed the presence of Lewy bodies in the brain stem and sympathetic ganglion. Conclusion: In our cohort, atypical MSA with temporal lobe degeneration was diagnosed antemortem and had long disease duration. Pathologically, NCI distribution was prominent in limbic systems but was spread to the frontal cortex, basal ganglia, and brainstem to a varying degree.
Dynactin is involved in Lewy body pathology

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Introduction: Dynactin forms a protein complex with dynein and the complex transports cargo retrogradely along microtubules. Dysfunction of the dynein-dynactin complex causes several neurodegenerative disorders, such as Perry syndrome. Recently, we reported colocalization of phosphorylated alpha-synuclein (p-SCNA) and the largest subunit of dynactin (DCTN1) in Lewy body-like structures in Perry syndrome. However, the relationship between dynactin and synucleinopathies has not been clarified. In this study, we examined the possible involvement of the dynein-dynactin complex in synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Methods: We examined 13 autopsied human brains of patients with synucleinopathy (5 PD, 5 DLB and 3 MSA). Immunohistochemistry for p-SNCA, DCTN1 (dynactin) and DYNC1I1 (dynein) was performed. We also examined microtubule affinity regulating kinases (p-MARKs), which phosphorylate microtubule-associated proteins and trigger microtubule disruption. Double immunofluorescence was also performed. Results: Both brainstem and cortical Lewy bodies were immunopositive for DCTN1, DYNC1I1 and p-MARK and their stainings often overlapped with p-SNCA. Lewy neurites were also immunopositive for DCTN1 and DYNC1I1. However, p-SNCA-positive inclusions of MSA such as glial cytoplasmic inclusions and neuronal cytoplasmic inclusions were negative for DCTN1, DYNC1I1 and p-MARK. Conclusion: Our results suggest that dynactin is closely associated with Lewy body pathology. In addition, immunohistochemistry for dynein-dynactin complex molecules, especially DCTN1, can distinguish Lewy bodies clearly from neuronal cytoplasmic inclusions of MSA.
The Lewy body pathology of pedunculopontine nucleus in Lewy body disease with postural abnormality

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Introduction: Pedunculopontine nucleus (PPN) is considered as responsible lesion for postural abnormality of Lewy body disease (LBD). Our aim is to evaluate the severity of Lewy body pathology of PPN in autopsy cases of LBD between with and without postural abnormality.

Methods: From the autopsy cases registered at our hospital, we used 17 consecutive autopsy cases that had been pathologically diagnosed with LBD. The location of PPN is identified by anti-CHAT antibody staining at 2 sections between red nucleus and locus ceruleus in brainstem. Phosphorylated alpha-synuclein staining was performed and the Lewy body pathology grading was evaluated according to the 4th DLB consensus guideline. Results: The mean age at death was 76.8 ± 9.3 (mean ± SD) and the mean age at onset of LBD was 63.3 ± 11.0. Five cases clinically showed postural abnormality, camptocormia and/or dropped head. About the Lewy body type pathology, 10 cases were neocortical type, 6 cases were limbic type and 1 case was brainstem type. The mean grade of Lewy body pathology in PPN of cases with postural abnormality was higher than that without postural abnormality. There was a tendency of more severe Lewy body pathology in the cases with postural abnormality, although there is no significant statistical difference. Conclusion: LBD patients with postural abnormalities tended to have more severe Lewy body pathology in PPN. There is a possibility that Lewy body pathology of PPN is related with postural abnormality of LBD.
An autopsy case of Parkinson's disease with RecNcil (L444P- A456P- V460) glucocerebrosidase gene (GBA) mutation

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Introduction: Mutations of beta- glucocerebrosidase gene (GBA) are known as a risk factor for Parkinson's disease (PD). It was reported that clinical features of PD with GBA mutation (GBA- PD) were rapid progression of motor symptoms and severe non-motor symptoms in their clinical course, while pathology of GBA- PD was not different from PD without GBA mutation. We describe a first autopsy report of GBA- PD with RecNcil (L444P- A456P- V460) GBA mutation.

Clinical Summary: A 68- year- old man noticed gait disturbance and frozen gait. REM sleep behavior disorder and hallucination occurred after one year of the onset. On hospital admission at the age of 70, the neurological examination disclosed Parkinsonism, autonomic failure, hallucination and dementia. UPDRS- III score and MMSE revealed 16 and 19 points respectively. The DNA analysis of the GBA gene revealed RecNcil (L444P- A456P- V460) mutations. His symptoms deteriorated rapidly, and died of pneumonia at the age of 73.

Pathological findings: The brain weight was 1056g pre- fixed. Loss of pigmentation from substantia nigra and locus ceruleus were found, and microscopic examination revealed that neuronal loss with reactive astrocytosis in these structures, as well as dorsal nucleus of vagus, nucleus basalis of Meynert and amygdala. Numerous Lewy bodies were found as 'diffuse neocortical type' of third DLB consortium criteria. The severity of concurrent NFT was mild (Braak state I), and no amyloid plaque was found.

Conclusion: In this case, cardinal hallmark of dementia was considered as the pure acceleration of alpha- synuclein, and independent from Alzheimer pathology.
Submandibular gland is useful for diagnosis of Lewy body disease- the first report from Japan

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Introduction: Pathological diagnosis of Lewy body (LB) disease (LBD) is based on the presence of LB-type α-synucleinopathy (LBAS) at autopsy. We already reported that skin biopsy is useful to detect LBAS. In this study, we tried to calculate sensitivity and specificity of LBAS in submandibular gland (SG) in Japanese, to support the study now conducted in US.

Methods: We retrospectively examined LBAS of SG in 175 consecutive autopsy cases, who had intracytoplasmic LBAS in the central nervous system and evaluated sensitivity. Next, we prospectively examined LBAS of SG in 34 consecutive autopsy cases to check specificity.

Results: The employed 174 cases were classified into 60 cases of the Brain Bank for Aging Research (BBAR) LB Stage II, 16 cases of Stage III, 55 cases of Stage IV, and 43 cases of Stage V. LBAS was detected in 38 (63.3\%) of Stage II, 13 (81.3\%) of Stage III, 41 (74.5\%) of Stage IV, and 35 (81.4\%) of Stage V. Thus, the sensitivity was 73.0\%. The prospectively studied cases included 23 cases of BBAR LB Stage 0, 4 cases of Stage 0.5, 1 case of Stage I, 1 case of Stage II, 1 case of Stage II, 3 cases of Stage IV and one case of Stage V. Among these, LBAS was found in all the cases of Stage II to V and no LBAS was found in Stage 0 to I. Thus, the specificity was 100\%.

Conclusion: This study confirmed usefulness of SG biopsy for diagnosis of LBD in Japanese.
Clinicopathological characteristics of pure type Lewy body disease with dementia

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Introduction: Very few studies referred to which component of dementia symptoms were associated with concomitant Alzheimer pathology in Parkinson's disease with dementia (PDD)/ dementia with Lewy bodies (DLB). This study aimed to clarify clinicopathological characteristics of pure type Lewy body (LB) disease with dementia (i.e. neuropathologically confirmed PDD or DLB cases without significant other neurodegenerative or vascular changes). Methods: Consecutive 820 autopsy cases from 2002 to 2013 in our institute included 79 PDD/ DLB cases. We excluded cases with significant senile changes (Braak neurofibrillary tangle stage, equal to or more than 3, plaque stage B and Saito's argyrophilic grain stage 2). We also excluded cases accompanied by symptomatic cerebrovascular disease, metabolic encephalopathy and other neurodegenerative diseases including progressive supranuclear palsy and corticobasal degeneration. Results: 10 cases were selected as pure PDD/ DLB. Male to female ratio was 6:4 and the average age at death was 82.9 years. The average brain weight was 1165g. Nine cases were classified into Braak LB stage 4 and the remaining one to Stage 5. Clinical diagnosis of five cases was PDD; two, DLB; two, Alzheimer disease (AD); and one, pure autonomic failure. Four cases died of pneumonia, four cases experienced unexpected sudden death, and another two cases died of cancer. Five cases had history of hallucinations and seven cases had truncal rigidity including neck. Conclusions: Our study highlighted difficulty in differential diagnosis of Lewy body dementia with AD. Our study also pointed out sudden death as a major cause of death in this group.
α-synuclein pathology in phrenic nerves of Lewy body disease. (In Japan)

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Introduction: Although restrictive respiratory disorder in Parkinson's disease is a clinical problem, the cause is not yet clear. Now, we focus on α-synuclein deposition in the phrenic nerve and compare it with systemic pathology. Methods α-synuclein deposition in the phrenic nerve and diaphragmatic intramuscular nerve (i.e. a more distal extension of the phrenic nerve) was assessed in 15 autopsied cases of Lewy body disease, and compared with the progression of Lewy body pathology throughout the body. Results: Average age of the 15 cases was 75.8 ± 8.8 years. Based on Brain bank for aging research (BBAR) staging criteria, 3 cases were stage 1, 2 were stage 3, 2 was stage 4, and 8 were stage 5. There was only 1 case that did not have α-synuclein deposits in phrenic nerves nor diaphragmatic intramuscular nerves. This case was BBAR stage 1. Six cases were positive in both nerves. The staging results for these cases; 3 cases were BBAR stage 5, 2 were stage 2 and 1 was stage 1. Five cases were positive in the phrenic nerve only; 3 cases in stage 5 and 2 cases in stage 3. In 3 cases, positive findings were found only in the intramuscular nerve; 2 cases were BBAR stage 5 and 1 was BBAR stage 1. Conclusion; α-synuclein deposition in the phrenic nerve of Lewy body disease can be observed from early stages on. The more advanced the systemic Lewy pathology, the more likely it is that positive findings are seen.
Acute swelling of medulla oblongata followed by sudden death in a case of MSA- C

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Introduction: We report a unique pathological change observed in a 59-year-old man with MSA. Clinical summary: His initial symptoms at age 50 were dysarthria and unsteady gait, followed by neurogenic bladder and dysphagia. Just prior to death, he was admitted to our hospital for aspiration pneumonia. Neurologically he presented with rigidity, cerebellar ataxia and myoclonus. MRI showed swelling in T1WI and high intensity in T2WI and FLAIR involving the medulla oblongata. Since his general condition was stable, he was discharged but visited the emergency ward ten days later. He died of acute respiratory failure. Pathological findings: The brain weighed 1.315g. Macroscopically cerebellum and brain stem was atrophic but medulla oblongata apparently preserved its normal size. Typical changes of MSA with glial cytoplasmic inclusions were present in putamen, substantia nigra, base of pons, cerebellar cortex, inferior olivary nucleus and spinal cord. In addition, swelling with severe vacuolar changes and axonal spheroids accompanying agonal hemorrhage involved medulla oblongata. Conclusion: This change may explain his unexpected death, but correlation with MSA may need further accumulation of similar cases.
Alpha-synuclein pathologies associated with deep brain stimulation in Parkinson's disease

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Introduction Deep brain stimulation (DBS) is a surgical treatment for advanced and complicated Parkinson's disease (PD). Alpha-synuclein (a-syn) pathologies of PD with DBS has been reportedly various. We will present a-syn pathologies of two cases of autopsied PD with DBS.

Clinical summary Two patients were sporadic and typical PD with severe wearing off and dyskinesia. Bilateral DBS leads had been previously implanted in the subthalamic nucleus (STN) for both patients. DBS was very beneficial for motor complications and kept good conditions over ten years.

Pathological findings The pathologies of two patients showed degeneration in the substantia nigra, locus ceruleus, and dorsal motor nucleus of vagus, and Lewy pathologies. Stagings of Lewy pathologies were limbic type and Braak stage 4. One patient showed a-syn pathologies around the DBS electrode incision, and another showed oligodendroglial a-syn pathologies along electrode of DBS.

Conclusion We experienced a-syn pathologies associated with DBS. Relationship between DBS and a-syn pathologies is still controversial. Our two cases may bring important information about mechanism of a-syn accumulation in patients with DBS.
Oxidative stress and uric acid are associated with pathomechanism of multiple system atrophy

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Introduction: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder and oxidative stress may partly contribute its pathogenesis. Uric acid protects neurons in neurodegenerative disorders via antioxidative effects. The aim of this study was to investigate the pathological relationship between uric acid and dityrosine, a marker for oxidatively modified proteins, in MSA. Methods: In this study, using specific monoclonal antibodies against uric acid and oxidative stress marker, dityrosine, we performed an immunohistochemical analysis in sections of archival, formalin-fixed, paraffin-embedded brain materials of five MSA patients and two control subjects. Results: Dityrosine immunoreactivity was prominently observed in neurons, glia and perivascular areas in the cerebellum, inferior olivary nucleus and basal ganglia including putamen, all of which are related to the pathological lesions of MSA. However, it was not detectable in all of the neuronal cytoplasmic inclusions and glial cytoplasmic inclusions. Overall, uric acid immunoreactivity was weak in whole regions of MSA brain. By contrast, dityrosine immunoreactivity in the control cases was very weak or undetectable in the parenchymal cells including neurons and glia and control brains were totally more stained by uric acid than MSA. Conclusion: These pathological observations implicate the tyrosine oxidative stress in the pathomechanism of MSA.
Accumulation of prostease-resistant alpha-synuclein in the skin

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Introduction: We previously reported that phosphorylated α-synuclein (psyn) positive (Lewy body) LB-related pathology involved the cutaneous nerves in Lewy body disease (LBD). However, the sensitivity was insufficient to establish skin biopsy as a diagnostic tool for LBD. The aim of the present study was to analyze the accumulation of the protease-resistant α-synuclein in the skin. Methods: Cutaneous LB pathology was evaluated in retrospective autopsy cases of LBD (148 cases) and in biopsy specimens with clinically suspected LBD (7 cases) by immunohistochemistry, using α-synuclein antibody with pretreatment of Proteinase K (PK). Results: The PK-resistant α-synuclein was deposited in nerve fascicles mainly around blood vessels in LBD, but not in control subjects. Immunoreactivity of PK-resistant α-synuclein was more intense and was observed more frequently than that of psyn. The rates of skin PK-resistant syn positivity (%) at each CNS LB stage were as follows: 57.7% in incidental Parkinson’s disease (PD), 88.2% in PD and PD with dementia and 53.8% in dementia with Lewy bodies. In all CNS LB stages, PK-resistant α-synuclein had a higher positive rate than psyn. Conclusion: PK-resistant α-synuclein is more sensitive than psyn. These findings suggest that skin biopsies with PK-pretreated α-synuclein antibody is a useful tool in the diagnosis of LBD. We will further investigate by increasing the number of cases.
Diffuse Lewy Body Disease coexisting with Progressive Supranuclear Palsy pathology and partially co-localising tau and alpha-synuclein positive oligodendroglial inclusions

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Introduction: Neuronal alpha-synuclein deposits are the hallmark lesions of Diffuse Lewy Body disease (DLBD) whereas glioneuronal 4-repeat-tau accumulation defines Progressive Supranuclear Palsy (PSP). Rare cases of coexisting DLBD and PSP have been described, but the oligodendroglial pathology remains underappreciated in DLBD. Clinical summary: A brain bank donation from a 71 years old male was examined. He was diagnosed with Parkinsons disease 16 years ago and developed hallucinations, confusion and autonomic failure 6 years ago. Pathological findings: Histology showed widespread alpha-synuclein immunoreactive Lewy bodies and Lewy neurites in keeping with a mild neocortical subtype of DLBD. In addition there was prominent tau pathology with tangles, oligodendroglial coiled bodies and tufted astrocytes, showing selective tau-4-repeat immunoreactivity, in basal ganglia, midbrain and tectum of the pons. Interestingly, alpha-synuclein positive oligodendroglial inclusions were also seen, especially commonly in the pallidothalamic tract and the midbrain. These inclusions did not show the distribution and typical morphology of Papp-Lantos bodies seen in Multiple System Atrophy. Double immunofluorescence studies showed that some of these oligodendroglial alpha-synuclein inclusions co-localised with tau-positive coiled bodies. Conclusion: Concurrent alpha-synucleinopathy in a minority of PSP cases and DLBD with PSP-like pathology has been described separately. However, partial co-localisation of tau and alpha-synuclein in oligodendroglial inclusions in mixed DLBD and PSP pathology has not been previously demonstrated. The findings raise the question whether there is a pathogenic interaction between these distinct pathologies rather than a coincidental overlap.
An autopsy case of mitochondrial complex III deficiency with homozygous mutation c.157_158dup in TTC19 clinically presenting as spinocerebellar ataxia

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Objective:
To document the autopsy findings in a case of homozygous mutation c.157_158dup in TTC19 manifesting clinical features of spinocerebellar atrophy.

Clinical summary:
A 15-year-old Japanese male with subaverage intelligence and questionable consanguinity developed gait disturbance with dragging of the left foot. At the age of 38, he showed dysarthria and could walk only with assistance. He was admitted to our hospital at age 60. Neurological examination disclosed saccadic eye movements, gaze-evoked directional nystagmus, severely slurred speech, mild muscular weakness in the lower legs, and truncal and limb ataxia. The mini-mental state examination score was 0/30. Brain MRI demonstrated cerebellar atrophy and abnormal intensity in the bilateral putamen. Spinocerebellar ataxia was clinically diagnosed. Six months later, the patient died of pneumonia at age 61. His elder brother and two of his elder sisters had also shown gait disturbance and died in their forties or fifties.

Results:
The brain weighed 1370 g before fixation. The cerebellum showed diffuse atrophy with brownish discoloration of the deep white matter. The bilateral striatum was severely degenerated. Histologically, the cerebellar white matter, striatum and tegmentum of the brainstem showed symmetrical cystic changes with fibrillary gliosis and capillary proliferation. The inferior olivary nuclei and substantia nigra showed asymmetrical degeneration. The cerebellum showed severe Purkinje cell loss and Bergmann's gliosis. Genetic analysis using full exome sequencing revealed homozygous mutation c.157_158dup in TTC19, known to cause mitochondrial complex III deficiency.

Conclusions:
For differential diagnosis of spinocerebellar ataxia, TTC19 mutation should be included as a rare possibility.
Early central nervous system involvement in a V30M ATTR amyloidosis patient

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Introduction: Hereditary ATTR amyloidosis is a systemic amyloidosis caused by transthyretin (TTR) gene mutation. Patients with V30M gene mutation, the most common mutation worldwide, typically present a severe sensorimotor and autonomic polyneuropathy and rarely develop CNS symptoms. CNS involvement has been recently described in posttransplant patients, whose transplant extend their life expectancy, and older symptomatic patients. We report a young female patient with a symptomatic ATTR cerebral amyloid angiopathy (CAA). Methods: Clinical case retrospective analysis. Results: A 41-year-old female, V30M TTR carrier presented with severe nephrotic syndrome by the age of 38. The neurological examination at this point showed minor abnormalities consistent with small fiber neuropathy. Kidney biopsy revealed severe TTR amyloid deposition with negative immunoglobulins and complement deposition and the patient started treatment with TTR stabilizer (tafamidis). Three years later the patient reported transient focal neurological episodes (FNEs) (numbness of left face and arm; right arm paresthesia progressing rapidly to the right hemiface). Brain MRI showed subcortical white matter hyperintensities and subpial hypointense lesions in T2* sequencing suggestive of hemorrhagic nature. She had high ESR and anti-nuclear antibodies titles. A brain biopsy was performed to exclude CNS vasculitis and revealed severe leptomeningeal ATTR-CAA. The study for amyloid-beta showed small diffuse cortical deposits, with no vascular involvement. Patient was APOE4 homozygous. Conclusions: ATTR amyloidosis with V30M can have a severe and early CNS involvement. The relationship between different TTR mutations and clinical phenotype, and phenotypical variability within the same mutation remains unclear.
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Hereditary diffuse leukoencephalopathy with spheroid axons (HDLS): clinical and neuropathological analysis

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Introduction: HDLS is an autosomal dominant inherited rare disease. The clinical manifestation includes cognitive disorder, movement disorder et al. The white matter changes on MRI are sometimes nonspecific. Characteristic histology is white matter damage with spheroid axons and pigmented macrophages. CSF1R was the pathologic gene mutation.

Methods: 5 patients diagnosed HDLS with brain biopsy and/or gene analysis were collected and clinical history, neuroimaging, histology as well as genetic information were analyzed and compared. Results: 4 females and 1 male aged 25-47 year old were included. The durations of the disease varied from 9 months to 4 years. Clinical manifestations include cognitive disorder with or without psychiatric and behavior problems, movement disorders such as paralysis, parkinsonism, pyramidal tract destruction as well as dysarthria and numbness of limbs. MRI showed multiple peri-ventricular white matter lesions, some of which fused to patches. There was no enhancement of the lesions, but DWI hyper-intensity was obvious and persistent. Brain biopsy was done in 4 of them. Histology showed widespread white matter damage, especially axon destroy with spheroids axons which were stained by NF and Ub, but not Aβ and Tau. Macrophages accumulation with foamy and pigmented cytoplasm was seen. Neither inflammation nor demyelization was found. CSF1R mutation was found in 3 of them.

Conclusion: Small peri-ventricular white matter lesions in young dementia patients should be appreciated. Persistent DWI hyper-intensity of the lesion on MRI was typical. Characteristic histology and gene analysis were diagnosable.
Manipulation of retinal glutamate levels by overexpression of GLAST reduces retinal ganglion cell death in an experimental model of glaucoma

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Introduction: Glaucoma is a neurodegenerative disease of the eye and we are interested in protection of retinal ganglion cells (RGCs), a type of retinal neurons whose death causes blindness in glaucoma. In this study we have generated mice with overexpression of the glutamate aspartate transporter (GLAST) with the aim to examine if efficient removal of extracellular glutamate protects RGCs in an experimental model of glaucoma, the optic nerve injury (ONI) model.

Methods: A novel transgenic mouse line with overexpression of GLAST (GLAST Tg) was generated. GLAST Tg mice were healthy and viable. Following ONI, changes in retinal morphology was monitored in vivo by optical coherence tomography (OCT). The number of RGCs was determined by haematoxylin & eosin staining and retrograde labelling of RGCs.

Results: Increased GLAST expression in the retina was confirmed by western blotting. In vivo imaging by OCT showed that the thickness of the ganglion cell complex in GLAST Tg mice was greater than in WT mice following ONI. Consistently, the ONI-induced RGC death in GLAST Tg mice was lower than in WT mice. We found that the retinal oxidative stress level is suppressed in GLAST Tg mice compared with WT mice after ONI.

Conclusion: Modulation of glutamate levels in the retina is effective for preventing RGC death. Increasing GLAST function in the retina may be useful for treatment of glaucoma.
Microglia loss does correlate with axonal spheroids in adult-onset leukoencephalopathy with axonal spheroids

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Introduction: The pathogenesis of adult-onset leukoencephalopathy with axonal spheroids (ALAS) is debatable. Pathological studies have suggested a primary axonopathy with secondary demyelination. However, with the identification of mutations in CSF1R, which is important for microglial survival, ALAS has been considered as microgliopathy. In this study, we examine the correlation of microglial changes and axonopathy in ALAS. Methods: A total of 6 ALAS cases were studied. The white matter lesions were classified into 3 evolving stages: 1) white matter with numerous axonal spheroids in a background of well-myelinated fibers; 2) moderate loss of myelinated fibers with or without axonal spheroids; and 3) leukodystrophy-like pattern of severe confluent axonal and myelin loss. Digital images of these stages were taken using the Aperio system. Precise areas of interest from the digital images stained with LFB/HE, APP, HLA-DR, and NF were demarcated on the computer screen. The spheroids and the ramified microglia (HLA-DR) were semi-quantified and assigned score from 0-3. Results: We found a strong correlation between the preponderance of axonal spheroids and degree of microglia loss. In all areas with predominance of axonal spheroids, there is almost complete loss of ramified microglia (score 0-1). This finding is also apparent even in very small affected areas in the cortex and the white matter. Meanwhile cells with macrophage phenotype are present in Stage 2 and 3 but not in the Stage 1. Conclusions: Axonal pathology (i.e. axonal spheroids) is strongly associated with loss of ramified microglia, suggesting a morphological-genetic correlation in the pathogenesis of ALAS.
A 43-year-old male autopsy case of sporadic amyotrophic lateral sclerosis with a family history of spinocerebellar ataxia type 3/Machado-Joseph disease

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Introduction: The cause of amyotrophic lateral sclerosis (ALS) is still unknown. Transactivation response DNA binding protein 43 kDa (TDP-43) is, however, thought to play a pathomechanistic role of ALS and also found in spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). We report an autopsy case of sporadic ALS with a family history of SCA3/MJD. Clinical summary: The patient had a weakness of right leg at 41, followed by gait disturbance, weakness of arms, and dyspnea successively, and then admitted to our hospital at 43. His relatives had spinocerebellar ataxia, and his mother had been diagnosed with SCA3/MJD by gene examination. Physical examination revealed flaccid tetraparesis, fasciculations on extremities, and areflexia of both legs. He didn't have ophthalmoparesis, ataxia, or sensory disturbance. Intramuscular electromyography findings indicated systemic neuropathic changes. ALS was most suspected but not determined because he had no upper motor neuron signs. Considering inflammatory neuropathies, steroid puls therapy and intravenous immunoglobulin were performed but didn't succeed. He died of dyspnea 2.5 months later after admission. Pathological findings: Atrophies were observed at oculomotor, trochlear, abducent, and hypoglossal nerves, and ventral roots. Neuronal loss and gliosis were observed in trigeminal motor nuclei, trochlear and hypoglossal nuclei, and spinal anterior horns. Degenerations were observed in corticospinal tracts. Bunina body was found in remaining thoracic anterior horn cells. TDP-43 were found in spinal anterior horns, hypoglossal nuclei, and primary motor area. 1C2 immunoreactive intranuclear inclusions were found in pontine nuclei. Conclusion: We reported an autopsy case of sporadic ALS with neuropathological findings of SCA3/MJD.
Mutant SOD1 aggregates from human ventral horn transmit templated aggregation and fatal ALS-like disease

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Mutations in superoxide dismutase-1 (SOD1) are a common known cause of amyotrophic lateral sclerosis (ALS). ALS patients and transgenic model mice carrying mutant human SOD1 (hSOD1) develop aggregates of the protein in motor neurons. Previously we showed that in transgenic mice two strains of aggregates (denoted A and B) can arise. Inoculation of minute amounts of A or B aggregate seeds, prepared by centrifugation through a density cushion, into spinal cords of asymptomatic G85R-hSOD1 transgenic mice initiated spreading, exponentially growing templated hSOD1 aggregations concomitantly with premature fatal ALS (Bidhendi EE et al, JCI 2016). In contrast to the unstable G85R-hSOD1 variant mentioned above the D90A-hSOD1 mutation produces a stable protein with an essentially normal enzymatic activity (Andersen et al, Nat Gen 1995). Transgenic mice for the mutation are known to lose motoneurons. However, only homozygous mice die of ALS after an extended clinical course. Heterozygous D90A mice showed much less and later pathologic changes, with lifespans of 680 days. Herein we show that inoculation of the strain A and B seeds into lumbar spinal cord of heterozygous hSOD1 D90A tg mice at the age of 100 days resulted in premature fatal ALS-like disease around 250 and 350 days after inoculation, respectively. While control seeds inoculated mice or mice which had not been inoculated, became terminally ill after around 690 days. This supports our previous proposition that prion-like templated spread of hSOD1 aggregation could be the primary pathogenic mechanism, not only in hSOD1 transgenic models, but also in hSOD1-induced ALS in man.
Involvement of TGF-beta signaling-related proteins in formation of inclusions of adult-onset neuronal intranuclear inclusion disease

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[Objective] To clarify the significance of TGF-β-related proteins in formation of nuclear inclusions (NIs) in adult-onset neuronal intranuclear inclusion disease (NIID).

[Methods] We examined cerebral cortex (autopsied 5; biopsied 1) from 6 patients diagnosed pathologically as having NIID with CNS symptoms (symptomatic group) and 3 autopsied patients without CNS symptoms but having similar NIs (non-symptomatic group), as well as abdominal adipose tissue from 3 patients in each group, and skin biopsy specimens from another 7 patients with symptomatic NIID. We identified NIs by p62 immunolabeling, and performed double-labeling immunofluorescence for p62 and pSmad2/3 or Smurf2.

[Results] Glia with NIs appeared denser than neurons with NIs (p < 0.01), and no significant inter-group difference was evident (p = 0.95 for glia; 0.33 for neurons). All nuclei without NIs showed labeling for pSmad2/3. However, in the symptomatic and non-symptomatic groups, 16.0% and 13.9% of nuclei with NIs, respectively, showed no pSmad2/3 labeling, and these proportions were similar (p = 0.91). The proportion of Smurf2 and p62 double-labeled NIs in the cortex in the symptomatic group was significantly higher than that in the non-symptomatic group (76.0% and 28.0%, respectively, p < 0.01), and the proportions in the adipose tissue of both groups were not different (93.3% and 34.0%, respectively, p = 0.01). In the symptomatic individuals the proportions in the cortex (76.0%) and skin (87.5%) were similar.

[Conclusions] Thus, characteristic expression profiles of pSmad2/3 and Smurf2 suggests a role for the TGF-β-related proteins in the formation of NIs in adult-onset NIID.
The expression of CD3, oxidative cytotoxic molecule, and stress response proteins related to degeneration of Purkinje cells in multiple system atrophy, cerebellar type

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Introduction: The pathogenesis of multiple system atrophy, cerebellar type (MSA-C) remains unknown. MSA-C is characterized by damage mainly to cerebellum, especially Purkinje cells. The expression of CD3 as a marker for the morphological and functional analysis of cerebellar Purkinje cells, and the expression of oxidative cytotoxic or protective molecules of the Purkinje cells under MSA-C stress were studied. Methods: This study was carried out on brain tissues from 17 patients with MSA-C, 10 normal individuals and from 19 fetuses, three neonates, and eight infants. For immunohistochemical analyses the following primary antibodies were used: CD3, oxidative modification to cysteine sulfonic acid of cys111 in human copper-zinc superoxide dismutase (Ox-SOD1), and stress response proteins (SRPs) (27, 70 and 90). Results: In normal adult Purkinje cells, the cell bodies and dendritic arborization including primary to tertiary dendrites were positive to CD3. The statistical quantitative analysis revealed that the areas positive for CD3 in MSA-C disappeared in the order from tertiary dendrites toward the cell bodies, along with the disease progression. The CD3-expression pattern along with MSA-C disease progression was reverse to the development changes in CD3-expression pattern of Purkinje cells from fetus to adults. The Purkinje cells in MSA-C were positive to Ox-SOD1 and SRPs, although normal Purkinje cells from fetus to adult were negative. Conclusion: Purkinje cells in MSA-C were under control of oxidative cytotoxic or protective molecules, and were finally impaired from periphery toward the center of the Purkinje cell arborization, being reverse to development from fetal to infant on the CD3 expression.
Clinico-pathological analysis in two cases of Huntington's disease

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Introduction: Huntington's disease (HD) is neurodegenerative disease presenting chorea, dementia and other psychiatric symptoms. We analyzed clinico-pathological features in two cases of HD. Clinical summary: Case 1 was 79-year-old woman at death. Her father and one brother had similar symptoms. The initial symptom was chorea at the age of 74. After 4 years from the onset, she was diagnosed as HD. The number of CAG repeats was 41. Total clinical course was about 5 years. Case 2 was 66-year-old man at death. The initial symptom was change of character at the age of 53. His father, sister and nephew had similar symptoms. After 3 years from the onset, he was diagnosed as HD. The number of CAG repeats was 49. Total clinical course was about 13 years. Pathological findings: As common findings in Case 1 and 2, severe atrophy of caudate nucleus and putamen were noted with marked neuronal loss and intense gliosis. Immuno-histochemistry for the expanded polyglutamine (IHC for polyQ) revealed that dense intra-nuclear and granular intracytoplasmic inclusions were distributed in neurons in the central nervous system, including cerebral cortex, thalamus, pons, dentate nucleus. Conclusion: These two cases with HD were supposed to be caused by paternal transmission, although the age of onset was not young. The patterns of IHC for polyQ might shed light on the pathogenesis of our cases.
An autopsy case of late-onset slowly progressive spastic paraplegia with a large deletion mutation in KIAA0196

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Introduction: Hereditary spastic paraplegia (HSP) is a genetically heterogeneous disorder characterized by spasticity and weakness of the lower limbs. The typical pathology is dying back-type chronic degeneration of bilateral corticospinal tracts of the spinal cord. Case: A 77-year-old man with a 16-year history of slowly progressive spastic paraparesis was admitted due to infective endocarditis. He was known to have a large deletion in KIAA0196, which is the causative gene of hereditary spastic paraplegia type 8 (SPG8). He died of multiple organ failure and autopsy was performed. Pathological findings: The brain weighted 1,162 g. Multiple ischemic infarcts were detected mainly in the right middle cerebral artery territory. The Betz cells were preserved. Secondary degeneration from the recent infarcts involved the right medullary pyramis and the left cervical corticospinal tracts. Distinct from these recent changes, caudally accentuated mild pallor with myelin stain of bilateral pyramidal tracts was evident. Histologically, the lesion showed commensurate loss of axons without evident astrocytic or microglial reaction. This pathology is consistent with his clinical picture and typical for HSP. Conclusion: We report the first autopsy case of SPG8 with a large deletion in KIAA0196. Further autopsy studies may be required to elucidate the relationship between genetic abnormality and clinical and pathological phenotypes in HSP.
Introduction: The high incidence of amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia complex (PDC) has been known in the Kii Peninsula of Japan and on Guam. The recent reports have revealed accumulation of several proteins in the brains of patients with ALS/PDC on Guam. Methods: We neuropathologically examined the brains and spinal cords of 18 patients with Kii ALS/PDC (clinical diagnoses: 8 ALS and 10 PDC) in Hohara Village, the eastern focus of Kii ALS. Sections of these specimens were immunohistochemically stained with antibodies against four major proteins: tau, trans-activation response DNA binding protein 43 kDa (TDP-43), alpha-synuclein (αSyn) and beta/A4 amyloid (Aβ). Results: Tau pathology including neurofibrillary tangles and TDP-43-positive inclusions were observed in all 18 cases, mainly in the limbic system. Synuclein pathology was present in 14 cases (77.8%) and Aβ was accumulated in 13 cases (72.2%). Several neurons contained two or more proteins. They were pathologically classified into three subtypes according to the most prominent proteinopathy: the tauopathy-dominant type, the TDP-43 proteinopathy-dominant type, and the synucleinopathy-dominant type. Three subtypes shared the common characteristic tau pathology, which suggests they are pathologically continuous on a spectrum and different phenotypes of a single disease. Conclusion: We have concluded that ALS/PDC in the Hohara focus of the Kii Peninsula is a single disease characterized neuropathologically by multiple proteinopathy with tau dominancy. Whether the coexistence of the three proteinopathies was incidental or pathogenetically related remains to be clarified.
**P2-72**

**Isolated nigral degeneration not associated with α-synuclein pathologies in the familial Parkinson's disease with LRRK2 p.R1441H mutation**

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*Introduction* More than ten causative genes of hereditary Parkinson's disease (PD) were detected. LRRK2 is a causative gene for autosomal dominant familial PD. Their pathologies are very heterogeneous. Here we report the neuropathologies of familial PD with LRRK2 p.R1441H homozygous mutation in the region of southern Japan.

*Clinical summary* The patient was 74 years-old man. His parents were consanguineous marriage, and four of his siblings were PD. There was another family had members of PD in the same city. He was diagnosed PD at the age of 60 and medicated with levodopa. Response of levodopa was quite good, but diurnal fluctuation, levodopa induced dyskinesia appeared. He became bed-ridden on 73yo, and died of severe pneumonia.

*Pathological findings* Depigmentation of the substantia nigra (SN) was remarkable. Neuronal loss and gliosis only in the SN were observed. There were no Lewy pathologies and other pathological structures. The neuropathological feature of this PD was isolated nigral degeneration without Lewy pathologies (IND without LP).

The pathologies of the autopsied case of another family with LRRK2 p.1441H heterozygous mutation also showed same findings (data not shown).

*Conclusion* This is the new pathological phenotype of familial PD with LRRK2 p.R1441H mutation. Among pathologies of LRRK2 mutated PD, IND without LP were reported in the families with LRRK2 p.I2020T mutation. The cases with homozygous and heterozygous LRRK2 p.R1441H mutation showed also IND without LP. This is the new pathological variation caused by LRRK2 p.R1441H mutations.
P2-73

Immunohistochemical Analysis of Nna1 in the Ataxia and Male Sterility (AMS) Mouse, an Nna1 Mutant and Model of Cerebellar Ataxia

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Introduction: Nna1 is phylogenetically-preserved and codes for cytosolic carboxypeptidase 1. Different Nna1 mutations are known to cause the progressive loss of Purkinje cells (PCs); thus models of cerebellar ataxia, and different modes of cellular degeneration/loss depend on the cell types. Our AMS mouse harbors a point mutation and is the only Nna1-allele model for which the genotype can be determined through a combination of restriction-enzyme digestion and PCR. We applied immunohistochemistry using anti-human Nna1 antibody to investigate its distribution in the cerebellum of AMS mice of each genotype from postnatal days (P) 7-28. Results: 1. Both the molecular and granular layers were positive for Nna1 in wild-type mice. The positivity peaked on postnatal day P7, before the maturation of the PC dendrites, and decreased thereafter. The PC somata and dendrites were clearly positive on P15, when dendritic innervation starts by the climbing fibers, to P28. 2. In ams-homozygous mice, PCs showed the same positive pattern as the wild-type mice. The semi-quantification of the Nna1’s stain-strength revealed in the following order: wild-type, ams-heterozygous, then ams-homozygous. Conclusion: The distribution of the Nna1 in the cerebellum, except in the PCs, of wild-type mice varies according to the age of the mice, while that in the PCs is stable from P15. The Nna1-mutated protein is present in AMS heterozygous or homozygous mice. The loss of PCs in homozygous AMS might occur due to a protein shortage because of the instability of its 3-dimensional structure, which is caused by the point mutation.
Brainstem calcification and extensive white matter changes in an autopsy case of bilateral striopallidodentate calcification with Alzheimer's disease

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Introduction: Bilateral striopallidodentate calcification, also known as Fahr's syndrome, is a rare but well-known neurological disorder characterized by extensive symmetrical brain calcification, specifically in the basal ganglia and cerebellar dentate nuclei. In most cases, brain calcification is detected by computed tomography; thus the brainstem calcification and white matter changes have not been described well. Clinical summary: The patient suffered from dysarthria diagnosed as cerebrovascular insufficiency with cerebral calcification at 65 years of age. She developed mild dementia at 75 years of age and Parkinsonism at 76 years of age. She became assisted with daily activities at 77 years of age. She became severely demented and a bed-ridden state at 82 years of age. She survived two years with tube feeding and died of lung cancer at 85 years of age. Computed tomography revealed symmetrical extensive intracranial calcification and severe cerebral atrophy, however, brainstem calcification was not detected. Pathological findings: Alzheimer's disease pathology and massive vascular calcification in the basal ganglia and dentate nuclei of the cerebellum were found. In addition, the vascular calcification continuously spread over the surrounding white matter and occasionally into the cortex (the depths of cerebral cortical sulci and cerebellar folia). In the brainstem, the calcification was extensive in the medulla and pontine tegmentum. Conclusion: We found severe vascular calcification in the brainstem. We also clarified the continuity of the vascular calcification through the white matter to the cortex. We should recognize brainstem calcification and extensive white matter changes in bilateral striopallidodentate calcification.
Amyloid beta-induced lysosomal impairment in retinal pigment epithelium contributes to the pathogenesis of dry age-related macular degeneration

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We have reported that Intracellular amyloid beta (Aβ) in retinal pigment epithelium (RPE) has been implicated in the pathogenesis of age-related macular degeneration (AMD). Herein we demonstrate that lysosomal impairment by Aβ contributes to autophagic cell death in RPE as a possible pathogenesis of dry AMD. First we found out that intracellular Aβ induces non-apoptotic cell death in a dose dependent manner. Dysfunction of autophagic flux by Aβ leaded to autophagic cell death. In addition, Aβ induced lysosomal depletion as well as mitochondrial depletion. Inhibition of Aβ uptake by blocking RAGE or enhancement of autophagic flux with rapamycin effectively rescued RPE from Aβ induced cell death. In vivo, intravitreal injection of Aβ induced autophagy and cell death. Rapamycin prevents Aβ induced RPE degeneration in mouse. In conclusion, Aβ induced dysregulation of autophagy (lysosomal impairment) and autophagic cell death in retinal pigment epithelium. We suggested autophagic dysfunction by Aβ as a pathogenesis of dry AMD.
Dry age-related macular degeneration like pathology in aged 5XFAD mice: Ultrastructure and microarray analysis

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Extracellular deposit of amyloid beta (Aβ) is a common pathologic feature in both age related macular degeneration (AMD) and Alzheimer disease, but the role of intracellular Aβ on the tight junction of the retinal pigment epithelium (RPE) had not been well investigated. Recently, we reported that intracellular Aβ42 could play a role in the breakdown of the outer blood retinal barrier in 5XFAD mice. Based on our hypothesis that 5XFAD mice, an animal model of Alzheimer disease, presents an accelerated accumulation of Aβ in the eyes as well as the brain could be a mouse model of dry AMD, we found out that aged 5XFAD mice can be used for dry AMD mouse model. The ultrastructure of RPE of 5XFAD mice was analyzed using transmission electron microscopy. Of importance, the aged 5XFAD mice show ultrastructural changes in the RPE and Bruch membrane (BM) that are compatible with the cardinal features of human dry AMD, including a loss of apical microvilli and basal infolding of the RPE, increased BM thickness, basal laminar and linear deposits, and accumulation of lipofuscin granules and undigested photoreceptor outer segment laden phagosomes. In microarray based analysis, the RPE complex of the aged 5XFAD mice shows differential gene expression profiles consistent with dry AMD in the inflammation response, immune reaction pathway, and decreased retinol metabolism. Taken together, we suggest that aged 5XFAD mice can be used as a mouse model of dry AMD to study Aβ related pathology and develop a new therapeutic approaches.
The role of KIF1C in sustainable myelination in SPG58/SAX2

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Hereditary spastic paraplegias (HSPs) are heterogeneous human neurodegenerative diseases. Mutations of genes encoding motor kinesins have been involved in various HSP isoforms. Mutations in KIF1C are responsible for autosomal recessive spastic paraplegia type 58 (SPG58/SAX2). Bovine progressive ataxia was first described in the Charolais breed in the early 1970s in England and further cases in this breed were subsequently reported worldwide. We can now report that progressive ataxia of Charolais cattle results from a homozygous single nucleotide polymorphism in the coding region of the KIF1C gene. In this study, we show that the mutation at the heterozygous state is associated with a better score for muscular development, explaining its balancing selection, and the resulting high frequency (13%) of the allele in the French Charolais breed. We demonstrate that the KIF1C bovine mutation leads to a functional knock-out, therefore mimicking mutations in humans affected by SPG58/SAX2. The functional consequences of KIF1C loss of function in cattle were also histologically evaluated. We showed that demyelinating plaques were due to altered oligodendrocyte membrane protrusion, and we highlight an abnormal accumulation of actin in the core of demyelinating plaques, which is normally concentrated at the leading edge of oligodendrocytes during axon wrapping. The lesions were associated with abnormal extension of paranodal sections. This model highlights the role of KIF1C protein in preserving the structural integrity and function of myelin, since the clinical signs and lesions arise in young-adult Charolais cattle. This model provides useful information for SPG58/SAX2 disease and other demyelinating lesions.
An autopsy case of SPG11 with peculiar p62-immunopositive intracytoplasmic inclusions

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Introduction: SPG11 is an autosomal recessive inherited spastic paraplegia with thin corpus callosum. Biallelic mutation in the SPG11 gene can also cause juvenile-onset amyotrophic lateral sclerosis-5 (ALS5) and Charcot-Marie-Tooth disease type 2X (CMT2X), different neurodegenerative disorders with overlapping features. Here, we report an autopsy case of SPG11 with IVS18+1G>T homozygous mutation. Clinical summary: At 27 years of age, the patient developed lower limb spasticity, and the symptom gradually worsened. Her elderly brother also suffered to same symptom. By age 44 years, she was wheelchair-bound and severely demented. She died of esophageal perforation at the age of 57 years. A cardiac uptake of 123I-metaiodobenzylguanidine is reduced, suggesting the cardiac sympathetic denervation. Autopsy findings: The brain weighed 786g. Severe cerebral atrophy and thin corpus callosum were noted. Histologically, large intracytoplasmic eosinophilic granular structures with vacuoles were observed in spinal root ganglia. Many coarse eosinophilic granules are also noted throughout the CNS. These eosinophilic structures are highlighted by immunohistochemistry for p62, but negative for p-TDP43 and p-tau. Additionally, rather small p-TDP43 positive neuronal inclusions are observed in the brain and spinal cord, however, no skein-like inclusions were detected. Neuronal loss of substantia nigra was severe. Tyrosine hydroxylase-positive nerve fibers were markedly diminished at the pericardium. Conclusion: The autopsy findings demonstrated that SPG11 involved widespread neuronal structures: cerebral cortex, corticospinal tracts, extrapyramidal nuclei, and peripheral nervous system including sympathetic nerves. Large eosinophilic bodies in the spinal ganglion cells with vacuoles may be most notable characteristic feature of SPG11. p-TDP43 depositions were also widely observed.
P2-79

**Selective autophagy eliminates ALS-related mutant SOD1 protein in cultured microglia**

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Background: Gain-of-toxic function of mutant SOD1 protein is thought to be responsible for motor neuronal death and formation of aggregates or inclusions in motor neurons and astrocytes. However, there is currently no available data on how microglia, in contrast to motor neurons and astrocytes, remain spared from mutant SOD1 toxicity and aggregate formation. Methods: We generated pcDNA3-Venus-tagged human wild-type and fALS-related A4V and G93A mutant SOD1 constructs. We then transfected these plasmids to mouse microglial cell line and examined their effects on cell toxicity and aggregate formation by immunohistochemistry, western blot and ELISA. Results: Immunocytochemistry showed that the transfected fALS-related mutant SOD1 proteins were barely detectable, whereas transfected wild-type SOD1 proteins were detected in cultured microglia. Westernblot and ELISA analyses revealed that mutant SOD1 protein levels were markedly reduced compared to those of wild-type SOD1 in microglia. The levels of mutant SOD1 protein were increased by the treatment with autophagy inhibitors. Immunocytochemistry showed that wild-type SOD1 protein was expressed in the cytoplasm and nucleus, whereas mutant SOD1 proteins were colocalized with the autophagy-related proteins p62 and LC3. Moreover, colocalization of these mutant SOD1 proteins with the selective autophagy related protein WDFY3 was observed. Additionally, wild-type SOD1 and mutant SOD1 proteins were released directly to the extracellular culture media from microglia. Conclusions: Our results provide in vitro evidence for degradation of mutant SOD1 protein by selective autophagy, which could have a protective effect on microglia during the pathological processes of ALS.
Neuropathological investigation of the nucleus accumbens focusing on clinical heterogeneity in Huntington disease

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Introduction: Huntington disease (HD) is an autosomal dominant neurodegenerative disorder characterized by chorea, psychiatric symptoms, and dementia. The prominent neuropathological feature is loss of neurons in the striatum, and motor symptoms are thought to correlate with the degeneration of the striatum. But the neuropathological background of psychiatric symptoms has been unknown precisely yet. The ventral part of the striatum is known as the nucleus accumbens (Acb), that is ROI as one of responsible focus of psychiatric symptoms. The purpose of the present study was to investigate the relationship between the neuronal changes in the Acb and clinical symptoms in HD.

Methods: The brains of 16 HD patients (3 behavioral/personality change onset (mean age at death/duration(years):46.0/21, HD-P), 13 motor onset (mean age at death/duration:64.2/16, HD-M)) and 4 control subjects (mean age at death:45.8) were investigated. Numerical cell densities for each of the large and small striatal neurons, and the ratio of small to large striatal neurons (S/L) in the Acb, caudate nucleus and putamen were determined.

Results: In HD brains, the small neuronal depopulation in the Acb was less than in the caudate and the putamen. Their neuronal depopulations were significantly greater than those of the controls (P=0.01). There was significant increase in the large striatal neuronal number in the Acb of HD-P compared to that of HD-M (P=0.04).

Conclusion: The pattern of the pathological changes of the Acb might be differed between in HD-P and HD-M. Some psychiatric symptoms in HD may be attributable to the degeneration of the Acb.
An autopsy case of malignant lymphoma associated with severe motor neuron degeneration

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Introduction: Extracranial malignant lymphoma was rarely reported to involve spinal motor neurons. The invasion and remote effects of lymphoma could be major causes of the conditions, but the pathomechanism is unknown. We report an autopsy case of malignant lymphoma with severe motor neuron degeneration. Clinical summary: A 70-year-old male had weight loss and exertional dyspnea when he was 68. 15 months later, he began to show atrophy in the upper extremities. 4 month after atrophy, he had dysarthria. He was hospitalized due to CO₂ narcosis and underwent respirator one month after his dysarthria. Electromyogram showed active denervation potentials in all extremities, which was consisted with Awaji criteria of ALS. Computed tomography revealed bilateral adrenal tumor. These tumors grew up rapidly, he died of insufficiency 2 months after adrenal tumor was detected and 8 months after muscle atrophy was found. Pathological findings: Brain weight was 1370g. General pathology showed swelling of bilateral adrenal grands and dorsal roots of spinal cord. Adrenal grands had massive atypical lymphocyte infiltration, which was consisted with diffuse large B cell lymphoma (DLBCL). Neuropathologically, lymphoma cells infiltrated dorsal root ganglions and dorsal roots. There was a severe neuronal loss in the anterior horns, especially in cervical spinal cord. Lateral columns of the spinal cord were preserved. Bunina bodies was not observed. TDP-43 positive cytoplasmic granules were revealed in the remaining motor neurons. Conclusion: We report the DLBCL case which was clinically mimicking ALS and presented severe motor neuron degeneration with TDP-43 positive granules.
Dynamic changes in microglia along with progression of lesion stages in ALSP and Nasu-Hakola disease

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Introduction: Adult onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), formerly hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS), and Nasu-Hakola disease (N-HD) are neurodegenerative diseases involving brain white matter and showing axonal spheroids. Both diseases are considered to be caused by dysfunction of microglia induced by different genetic defects. Methods: The brains of Japanese ten patients with ALSP and eight patients with N-HD and five age-matched controls were examined neuropathologically with special reference to lesion staging and dynamic changes of microglial subsets. Results: In ALSP, four lesion stages based on the degree of axon loss were discerned by the authors. Stage I, patchy axon loss in the cerebral white matter without atrophy to Stage IV, devastated cerebral white matter with marked dilatation of the ventricles and axon loss in the brainstem and/or cerebellum. In N-HD, similar stages were elucidated, but the internal capsule and pontine base were relatively well preserved in the N-HD, even at Stage IV. In microglial cells, the shape, density and immunopositivity for CD68, CD163 or CD204 were changed along with the progression of the stages in both diseases. Conclusion: The shape, density and subsets of microglia change dynamically along with the stages in the brain lesion in both diseases, and microglial changes precedes loss of axons in ALSP.
Familial amyotrophic lateral sclerosis with SOD1 Leu126 Ser mutation - clinical and pathological studies

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Introduction: Familial amyotrophic lateral sclerosis with L126S mutation in copper/zinc superoxide dismutase (SOD1) gene is only reported in Japan. One atypical case was presented in the literature.

Method: We clinically and pathologically studied five autopsied cases of this mutation in our brain bank network with the Brain Bank for Aging Research (BBAR) ALS protocol and pursue genotype-phenotype correlation.

Results: The mean age at onset and duration was 51.6 years old and 8.9 years, respectively. All the cases did not present upper motor signs and four out of five cases first experienced weakness of lower extremities. Neuropathologically, all cases showed neuronal loss of spinal anterior horn and hypoglossal, facial and trigeminal motor nuclei. Betz cells were mildly affected with occasional neuronophagia. Neuronal loss involved Clarke's column with degeneration of posterior spinocerebellar tracts and middle root zones of the posterior column. Lewy body-like hyaline inclusions were very few and basophilic inclusions with eosinophilic fibrillary stain were observed, each corresponding immunocytochemically to the epitope of phosphorylated neurofilament and SOD1. Ultrastructurally the inclusions showed ten nanometer filaments with side arms, mixed with granulofilamentous profiles.

Conclusion: FALS with L126S mutation in SOD1 gene clinically showed slowly progressive lower motor neuron disease. Accumulation of SOD1 among neurofilamentous accumulation exhibits with unique morphology of the affected neurons.
Comparison between measurement results of spinal fluid biomarkers and autopsy findings

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Introduction: Cerebrospinal fluid (CSF) human tau (hTau), phosphorylated tau (pTau), and amyloid β (Aβ) are regarded as good biomarkers for Alzheimer's disease (AD). We began measuring the levels of these biomarkers in our patients in 2010, of which six have undergone autopsy. Here, we reviewed the presence of CSF biomarkers in relation to the autopsy pathological findings. Methods: The pathological diagnosis of the included patients was as follows. Case 1 involved an 86-year-old man with combined AD and Dementia with Lewy bodies. Case 2 involved an 83-year-old female with combined myelopathy and AD. Case 3 involved a 62-year-old female with a 10-year history of multiple system atrophy. Case 4 involved a 74-year-old female with amyotrophic lateral sclerosis. Cases 5 and 6 involved 77-year-old and 88-year-old males, respectively, with progressive supranuclear palsy. Results: In case 1, Aβ was 334 pg/mL (standard: >500 pg/mL). In case 2, hTau was 1234 pg/mL, while pTau was 110 pg/mL (<300 pg/mL, <50 pg/mL) and Aβ was 470 pg/mL. In cases 3 and 5, Aβ was low (368 pg/mL and 415 pg/mL, respectively). In case 4, hTau was high, at 613 pg/mL. In case 6, these biomarker levels were within the reference range. Conclusion: The presence of CSF biomarkers in all cases was consistent with pathological and clinical findings, including AD pathology, myelopathy, progression of rapid pathological conditions, and activity of daily living. Thus, comparison with autopsy findings can be used to determine the accuracy of CSF biomarkers.
An autopsy case of familial adult-onset neuronal intranuclear inclusion disease (NIID), with clinical differential diagnosis mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

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Introduction: Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disease characterized by eosinophilic hyaline intranuclear inclusions (NIs) in neuronal and somatic cells. In general adult-onset cases show dementia with leukoencephalopathy. We describe an autopsy report of NIID with repeated stroke-like episodes. Clinical summary: A 62-year-old man with intense family history of dementia and stroke or encephalitis presented with left hemispacial neglect, high fever, and left hemiparesis. 2 years later dysphagia, dysarthria and right hemiparesis occurred. 6 years later he presented with aphasia following high fever. Brain magnetic resonance imaging (MRI) showed diffuse edematous lesion of left cerebral hemisphere. He died of aspiration pneumonia at the age of 72. Pathological findings: The brain weight was 1182g, pre-fixed. Macroscopically multifocal linear lesions in cortico-medullary junction, focal cortical atrophy, and softening in white matter (WM) were found. Microscopically laminar necrosis in deep layer of cortex, spongiotic change in cortico-medullary junction, and rarefaction and spongiosis of WM were seen. NIs, positive for ubiquitin and P62, were found predominantly in glial cells, compared to neurons. Large NIs were most frequently seen in Basal nucleus of Meynert, followed by thalamus and cerebral cortex. In the center and around spongiotic foci, there was little or no reactive astrocytes, while in the nearby WM, small number of bizarre shaggy-shaped astrocytes were observed. Conclusion: Main lesions seemed independent from the distribution of NIs, but seemed related to the insufficient reaction of astrocytes.
Leukoencephalopathy with vanishing white matter: Clinicopathological characteristics of a rare adult-onset case with a homozygous EIF2B5 mutation

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Introduction: Here, we present the clinicopathological characteristics of a rare autopsy case of adult-onset leukoencephalopathy with vanishing white matter (VWM). Clinical summary: A 64-year-old Japanese female with consanguineous parents exhibited irritability after delivering her son at the age of 38 years old. Two years later, cognitive impairment and hyperreflexia became evident following a traffic accident. A brain MRI study revealed severe rarefaction of the cerebral white matter with periventricular cysts, being more conspicuous in the frontal lobe. A gene analysis disclosed a homozygous missense mutation (T182M) in EIF2B5, establishing the diagnosis of VWM (Ohtake et al., 2004). She died of colon cancer at age 64.

Pathological findings: The brain weighed 950 g. In sections, the cerebral white matter showed severe atrophy and gelatinous appearance, with marked dilation of the lateral ventricles. Histologically, marked myelin pallor and axonal loss with spheroids were evident in the cerebral white matter. Distinct glial abnormalities including the appearance of bizarre-shaped astrocytes and foamy oligodendroglia were also a feature. Immunohistochemistry disclosed reduced expression of phosphorylated eIF2alpha in the astrocytes in the cerebral white matter and the ependymal cells lining the lateral ventricles. Conclusion: The present result suggests that in adult-onset VMW, presumably due to the dysfunction of eIF2B, phosphorylation of eIF2alpha and subsequent stress response are attenuated in the white matter astrocytes and ependymal cells, rendering the periventricular white matter susceptible to stress such as febrile infections and head trauma.
A comprehensive analysis of genetic variations and neuropathologic features of patients with PARK2

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Objective: To investigate PARK2 mutational variability and neuropathologic features of PARK2 patients.

Methods: We selected eight autopsied patients showing characteristic clinical symptoms, including juvenile parkinsonism, foot dystonia and sleep benefit. Dysesthesia of limbs was seen in 3 patients. A detailed molecular analysis using frozen samples of the cerebral cortex detected previously known and novel mutations in PARK2. We evaluated biochemical, immunohistochemical and histopathological features of the CNS tissue of these patients.

Results: Homozygous and heterozygous point mutations, p.C431F, were found in patient #1 and #2, respectively. Copy number variations were found in 7 patients. Patients #3 and #4 of a family carried the heterozygous deletion of exon 4. In patients #5, #7, #2 and #6, we found a homozygous duplication of exons 6-7, a homozygous duplication of exons 10-11, a heterozygous duplication of exons 2-4, and a heterozygous duplication of exon 2, respectively. Direct sequencing mRNA of patient #6 revealed a compound heterozygous mutation: triplication of exon2 and deletion of exons 2-3. Patient #8 harbored a compound heterozygous mutation: duplication of exons 2-4 and deletion of exons 3-4. Western blotting and immunohistochemistry revealed faint or no expression of PARKIN. In the substantia nigra, neuronal loss and relatively mild gliosis, accompanying the specific subfields involvement pattern, was evident. Lewy bodies were found in three patients. We found mild degeneration in the spinal dorsal root ganglia.

Interpretation: A genomic and mRNA analysis is needed to identify the precise PARK2 mutations. The patients harbored the variable mutations, but the clinicopathologic phenotype appears similar.
A case of idiopathic normal pressure hydrocephalus with Alzheimer's disease pathology, presenting good clinical outcome after ventriculo-peritoneal shunt

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Introduction: Idiopathic normal pressure hydrocephalus (iNPH) is treatable dementia caused by impaired dynamics of cerebrospinal fluid (CSF) and subsequent ventriculomegaly. Concomitant Alzheimer's disease (AD) pathology is reported to show poor clinical outcome after intervention.

Case Report: An 82-year old female, suffering from chronic cognitive decline, admitted to our hospital for a few-month history of rapidly progressive apathy, urinary incontinence, gait disturbance and failure of oral intake. MRI showed lesion of the white matter of Fazekas grade III with ventriculomegaly, mimicking Binswanger disease. After lumbar puncture, the symptoms definitely improved. The level of Aβ 42, tau, and phosphorylated tau in CSF were consistent with AD. PIB amyloid PET was also positive. We treated her with ventriculo-peritoneal shunt and sampled small pieces of cerebral cortex and white matter. After shunting, the patient's symptoms improved dramatically until now for two years. The white matter change and dilatation of the ventricles improved after the surgery.

Neuropathology: The sampled neocortex showed senile plaques of CERAD B level and the presence of definite neurofibrillary tangles, supporting Braak AT8 stage V. The white matter presented moderate diffuse astrogliosis alone.

Discussion and Conclusion: The MRI of this case can be classified into Binswanger type without DESH. This case may suggest that improved CSF dynamics override concomitant AD pathology at least two years and improved her quality of life.
Neuropathological findings of an autopsy patient with sporadic idiopathic basal ganglia calcification

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Introduction: Idiopathic basal ganglia calcification (IBGC) is a rare and intractable disease. We report a pathologically confirmed patient with sporadic IBGC. Clinical summary: An 83-year-old woman showed progressive personal change, and memory disturbance in the last 5 years. On admission, neurological examination showed akinetic mutism with no focal signs. Laboratory examination showed no abnormalities such as the serum level of Pi, Ca, and parathyroid hormone. Brain CT revealed frontotemporal atrophy and symmetric calcification in the bilateral basal ganglia, dentate nuclei, and white matter. SPECT showed decreasing regional cerebral blood flow in bilateral frontotemporal cortices. Three months later, she died due to pneumonia. Genetic analysis showed no mutation in the SLC20A2, PDGFB, PDGFRB, or XPR1 gene. Pathological findings: The brain weight at autopsy was 1,050g. Mild frontotemporal atrophy was recognized. Microscopic analysis revealed calcification in the bilateral putamen, striatum, dentate nuclei, and cerebral and cerebellar white matters. Senile changes were also shown as Braak stage II of neurofibrillary tangles (not diffuse), stage II of AT8 stained tau, and CERAD A or Braak A of senile plaque without argyrophilic grain, tufted astrocyte or astrocytic plaque. Conclusion: Although clinical findings of this patient were fulfilled with a probable item of diagnostic criteria for diffuse neurofibrillary tangles with calcification (DNTC), we made the diagnosis of sporadic IBGC using pathological analysis. The final diagnosis of this condition should be confirmed by the pathological findings.
Can we differentiate neuronal intranuclear inclusion disease from fragile X-associated tremor/ataxia syndrome?

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Introduction: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder in the FMR1 premutation carrier. Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disease characterized by the presence of eosinophilic nuclear inclusions (Nis) in the nervous system and visceral organs. We present for the first time the close similarities of clinical, neuroradiological and histopathological findings between FXTAS and NIID. Clinical summary: A 79-year-old man with FXTAS showed the characteristic features of NIID and striking similarities of MRI and skin biopsy findings between the patient and a case of NIID without the FMR1 premutation. They share key diagnostic features for each disease (FXTAS: high-intensity signal in the middle cerebellar peduncles on T2-weighted imaging, NIID: high-intensity signal along the corticomedullary junction on diffusion-weighted imaging, NIs in skin biopsy). We reviewed the clinical features of FXTAS and NIID, and found that almost all of the clinical manifestations and MRI findings of FXTAS were reported in patients with NIID. Pathological findings: Ultrastructural and immunohistochemical study of biopsied skin samples from these patients revealed NIs in the sweat gland cells, adipocytes and fibroblasts. The NIs found in both disorders are indistinguishable morphologically, and share immunohistochemical features. Conclusion: Even in the patient who satisfied diagnostic criteria for a definite FXTAS, it is possible to consider an incidental occurrence of NIID in the FMR1 premutation carrier. It is still undetermined whether the characteristic features of NIID are actually specific to NIID or also found in patients with FXTAS. Therefore, at present, we cannot differentiate NIID from FXTAS.
The Brains for Dementia Research cohort

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Wolfson Centre for Age-Related Diseases

Introduction: Brains for Dementia Research (BDR) was funded in April 2008 and is a programme of planned brain donation which provides high quality post-mortem brain tissue and clinical data from both those with and without memory impairment to researchers working in the field of dementia with the aim of finding new treatments and a cure for dementia. BDR comprises a network of 6 leading dementia research centres based at the Universities of Kings College London, Oxford, Bristol, Newcastle, Manchester and Cardiff and builds on established brain banks in the first 5 named.

Methods: Between 2009 and January 2018, 3,276 volunteers gave informed consent for brain donation and a total of 9,804 assessments have been completed to date. Assessments include collection of sociodemographic, cognitive and behavioural data. Following death, a full neuropathological report is produced including Braak tangle staging, Braak Lewy body score, Thal amyloid phase and CERAD stages. VCING probability is available for the majority of cases.

Results: Brains and associated data from over 600 deceased participants are available for researchers as is the assessment data on all participants. A total of 156 participants died with no cognitive impairment, 30 with MCI and over 400 with dementia with a median number of assessments per participant of 2. Within the living cohort, 72% have no cognitive impairment and further 9% MCI.

Conclusion: BDR represents a valuable cohort supporting worldwide dementia research.
Fukushima Brain Bank; Unique activity of Japanese private geriatric hospital

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Introduction: The Fukushima Brain Bank (FBB) was established under the auspices of the Fukushima Hospital (FH), managed completely within the private sector. We have several buildings for the aged and disabled, and about 800 elderly people reside in the area. The FH was established in 1982 and is managed by the Sawarabi Medical Cooperative. It currently has 487 beds. Our patients mainly have dementia and cerebrovascular problems. The hospital plays a pivotal role within the village and acts as the central facility. Methods: FBB was established in 1990. We have a long record of collecting samples from patients. This allows us as medical doctors and researchers to obtain clinical information or blood samples, sometimes even before the onset of illness. In our institute, all clinical and pathological data are held in the office of individual data management. Results: Although our bank has gone unrecognized in the past, our farsighted efforts have been gaining considerable attention in recent years in Japan. We now have over 20 collaborators and supply more than 30 research institutes with our samples. In 2017, we have 25 cases autopsies and delivered 12 institutes. Conclusions: Our research institute was approved in 2004 by the Ministry of Education, Culture, Sports, Science and Technology, as one of the non-governmental institutes which is permitted to apply for governmental grants and we became a member of the Comprehensive Brain Science Network in 2010. From 2016, we are receiving support from Platform of Supporting Cohort Study and Biospecimens Analysis Grant.
Standardization of frozen tissue resource- efforts at the National Center for Neuropathy and Neurology (NCNP) in Japan Brain Bank Net (JBBN)

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Introduction: Japan Brain Bank Net (JBBN) is AMED (Japan Agency of Medical Research and Development)- funded national consortium to accumulate postmortem brain resource. As the PI of JBBN, we propose the standard protocol of the resource built in NCNP.

Methods: We modified the BBAR (the Brain Bank for Aging Research) protocol (www.mci.gr.jp/BrainBank/). At autopsy, recovered brains are weighed, taken pictures, separated at junction of midbrain and pons and sagittally divided into half. More affected side of the brain with in vivo digital neuroimage is fixed in 20% buffered formalin for 7-13 days and prepared for morphological studies. Otherwise, fixed or frozen half is determined randomly. From the frozen half are obtained 7 mm thick consecutive coronal sections of the cerebrum, 5 mm thick sagittal sections of the cerebellum and 5 mm thick axial sections of the brain stem. After taking photos, small pieces of representative anatomical areas are fixed in 4% paraformaldehyde two overnight and served for morphological studies. The remaining tissues are rapidly frozen on plates of dry ice, covered by powdered dry ice. The frozen tissue is sealed in Zip-Lock® bags and stored at -80 degree. Results: JBBN employs RIN (RNA Integrity Number) for quality control and our method is comparable to other members. This method may be preferable to sandwich method of dry ice plate, which will put pressure on soft unfixed brains.
BRAIN UK: accessing NHS tissue archives for neuroscience research

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Introduction. Human tissue can be difficult for neuroscience researchers to access, with legal and ethical considerations challenging and time consuming. Prospectively collecting tissue for a study is expensive and may take many years, whereas Neuropathology archives in the UK National Health Service (NHS) contain a wealth of tissue collected over 40 to 50 years of diagnostic surgical and autopsy practice. About 500,000 cases, with 18,500 added annually, include tumour, muscle and nerve biopsies and diverse CNS disorders.

Methods. UK Neuropathologists, supported by the British Neuropathological Society, funded by the Medical Research Council and Brain Tumour Research, collaborate to form a national virtual brain bank. A linked-anonymised database includes diagnosis and simple demographics. BRAIN UK acts as a matchmaker and its generic ethical approval covers most projects via a straightforward application process (www.brain-uk.org).

Results. BRAIN UK reduces the time for researchers to achieve ethical approval and provides tissue via its network. 104 studies have been supported with almost 7,000 cases approved for release, resulting in 34 publications to date. Studies encompassed a wide variety of conditions including head injury, epilepsy, genetic and developmental disorders, psychiatric disorders, neuroinflammation and neurodegenerative disease. 40 tumour studies have been supported, providing large numbers of cases or rare tumour types, particularly highlighting the success of this approach.

Conclusion. BRAIN UK is a national virtual brain bank, facilitating access to under-utilised neuropathology archives to international researchers. Tissue that would otherwise be unused has supported valuable neuroscience research.
Neuronal expression of Toll like receptor 3 and its correlation with microglial activation and interferon gamma expression in human rabies

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Introduction: Rabies encephalitis is a significant health issue in Southeast Asia. Immune responses in human rabies are poorly understood. We earlier demonstrated a positive correlation between proinflammatory cytokines expression and degree of inflammation but not with rabies viral antigen load in brains of human rabies. However, the mechanisms that differentiate rabies infection into encephalitic form and paralytic form remain undetermined.

Methods: A retrospective study on 11 encephalitic and 7 paralytic post-mortem cases of human rabies was done. Extensive sampling from different regions of brain was performed and sections from hippocampus, pons and cervical spinal cord were subjected to immunohistochemistry using antibodies against rabies viral antigen, CD68, Toll like receptor 3 (TLR3) and Interferon gamma. Results: The inflammatory response was most marked in medulla, pons, spinal cord and hippocampus, especially in paralytic rabies cases. There was marked CD 68 positive microglial proliferation in all cases of paralytic rabies but it was seen in only 2 out of 11 cases of encephalitic rabies. Compared to diffuse cytoplasmic neuronal expression of TLR3 in paralytic rabies, the encephalitic form demonstrated perinuclear endosome like pattern. The intensity of IFN gamma expression was increased in paralytic rabies versus encephalitic rabies and it directly correlated with severity of CD68 positive microglial proliferation. Conclusions: The perinuclear pattern may indicate relocalization of TLR3 in endosomes and inclusion bodies, which may represent an evasive strategy of rabies virus. The sub-cellular localization of other TLRs will further shed light on immunopathogenesis and virus dissemination.
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Preliminary findings of the pathogenesis of central nervous system granulomatous inflammation in tuberculous meningitis in South Africa: a post-mortem immunohistochemistry study

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Introduction: Human post-mortem histopathological studies in tuberculous meningitis are lacking. The cellular composition and cytokine profile of granulomas in human neurotuberculosis have not yet been explored.

Methods: This retrospective study included patients diagnosed with central nervous system tuberculosis between 1975 and 2012 at Tygerberg hospital, South Africa. Histopathological assessment (Haematoxilin and Eosin, Ziehl-Neelsen and Reticulin staining), immunohistochemical techniques for cellular composition (innate and adaptive immune system) and cytokine profile of brain tuberculous granulomas were performed. These findings were correlated with the brain imaging.

Results: Eighty-three patients (40 <14 years, 43 ≥14 years of age) had a post mortem autopsy or brain biopsy performed. A total of 452 brain specimens were included. Three different types of granulomas were identified histologically and radiologically respectively: non-necrotizing (retic positive; T2WI iso-intense to the brain and uniform enhancement), necrotizing gummatous (retic positive; T2WI hypo-intense with ring-enhancement) and necrotizing abscess (retic negative; T2WI hyper-intense with ring-enhancement). Granulomas were perivascular located, mainly in the leptomeninges and superficial cortex. CD4 T-helper cells were absent in post-mortem specimens while present in biopsies. CD20 B-cells were present in lymphoid aggregates in the leptomeninges near the pia mater. Caspase-3 positive cells were not identified in these specimens.

Conclusions: The absence of CD4 T-helper cells and the presence of CD20 B-cells demonstrates the important role of the humoral adaptive immune response in tuberculous meningitis, whereas tuberculosis is a disease classically driven by a cellular adaptive immune response. Apoptosis does not seem to play a role in cell death in tuberculous meningitis.
A neuropathological and neurobiological study of brain malformations observed in fetuses infected by the Zika virus

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Introduction: Zika virus (ZIKV) fetopathy is associated to a high rate of congenital microcephaly with poor outcome. Our aim is to account a neuropathological description of brain anomalies in ZIKV fetopathy and to go further in the explanation of their pathogeny. Methods: Full fetal, neuropathological, neurobiological and placental analysis was performed in three fetuses after pregnancy termination between 22-25 weeks gestation for fetal ZIKV infection with brain malformation in accordance to French legislation. Results: All cases displayed severe neuronal deficit and damaged cells in association with characteristic lesions of meningoencephalitis. Neurobiological study performed on the supratentorial levels found abundant ZIKV particles and an excess of progenitor cells death with endoplasmic reticulum damages. Visceral and placental examinations showed no major changes, except for testicular inflammatory changes in male fetuses. Conclusion: Our study highlights the elective neurotropism of ZIKV. Interestingly, it permits us to identify a cascade of developmental defects associating a diffuse neuronal depletion due to an excess of progenitor cells damages to a severe brain atrophy resulting from a meningoencephalitis marked by diffuse vascular impairments.
PrPres deposition in the retina of sporadic, familial and iatrogenic Creutzfeldt-Jakob diseases

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Introduction: The purpose of this study is to analyze PrPres deposits of the retina. Methods: We analyzed the following cases in this study: 9 cases of SCJD (MM1), 2 cases of SCD (MM1+2), 1 case of SCJD (MM2), 3 cases of familial CJD (two of V180I and one of M232R), and 1 case of iatrogenic CJD (cadaveric dura mater graft). 5 control cases such as no neurological disease, Alzheimer disease, amyotrophic lateral sclerosis and multiple system atrophy were also used. For immunohistochemical studies to detect PrPres, monoclonal antibodies specific to prion protein 3F4 (109-112) and 12F10 (144-152) were used. The retinal sections were processed using a Ventana Discovery automated immunostainer. Results: In all CJD cases, 3F4 and 12F10 immunoreactive deposits (-irs) were consistently and clearly observed in the outer and inner plexiform layers (OPL and IPL) of the retina. PrPres-irs were coarse granular and fine synaptic patterns in the OPL and IPL, respectively. In some instances, fine granular PrPres-irs were seen in the inner and outer nuclear layers as well as in the nerve fiber layer. No PrPres-irs were present in the retina of control cases. Conclusion: PrPres-irs of the retina were consistently observed regardless of CJD cases. In addition to OPL and IPL, PrPres-irs may be widely observed in other layers of the retina.
Autophagy markers in dystrophic neurites in human and experimental prion diseases

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Dystrophic neurites (DNs) are abnormal neuronal processes characterized microscopically by aberrant sprouting, dystrophic expansion, and accumulation of various cellular organelles and cytoskeletal and signalling proteins. In human neurodegenerative diseases DNs are often located in the vicinity of amyloid plaques. However in experimental scrapie they are observed in the neuropil regardless of the absence of amyloid plaques. Despite decades of research, the mechanism underlying the development of DNs remains unclear. We performed electron microscopy, immunohistochemistry and confocal laser microscopy in brain specimens of hamsters infected with 139A scrapie strain as well as in post mortem human brains with prion diseases. Electron microscopy showed accumulation of autophagic vacuoles as well as autophagolysosomes in dystrophic neurites in human and experimental prion diseases. Confocal laser microscopy showed immunoexpression of p62 (SQSTM1) mainly in the perikarya and to a lesser degree in the processes of the neurons. Puncta of LC3 protein were present in both the cytoplasm and processes of some neurons in the human brains. In experimental scrapie LC3 immunoexpression showed mainly fibrillary pattern. Our study indicates that autophagy is a prominent feature of dystrophic neurites and that autophagy increase in neurons may be compartment-specific. This work was partly supported by Poland National Science Centre grant 2015/19/B/NZ4/03234
Difference between the immune pattern of granulomatous injuries in the lung and brain during infection with mycobacterium tuberculosis

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Tuberculosis (Tb) is the treatable infectious disease with the highest lethality in the world. Central Nervous tuberculosis (CNS-Tb) represent 1% of all Tb cases, and 5-10 % of extrapulmonary tuberculosis. Is the most devastating form of Tb, with a morbi-mortality upper of 50% and 30% of survivors develop sequels. The CNS is protected by the blood brain barrier (BBB), this confers immune privilege characteristics, hence, physiopathology studied on the periphery of the organism should not be applied to the CNS. We evaluated 16 cases with CNS-Tb diagnose to describe, identify and contrast the histological and immunological pattern of granulomatous lesions in brains versus lungs. Histological lesions and cell types present in sections of paraffin-embedded tissue from CNS and lung were identified; IL-1 $\beta$, IL-4, IL-6, TNF $\alpha$ e INF $\gamma$ detection was realized by immunohistochemistry. The most frequent granulomatous lesions in the CNS were the diffuse cellular accumulations, without central necrosis, unlike lung granulomas, which presented a circular, well-defined shape and central caseous necrosis. Regarding the expression of cytokines, in the CNS lesions, it was found that the positive response of the inflammatory cells was lower than in the pulmonary tissues. However, we found statistical significance in the expression of IL-1 $\beta$, IL-6 and TNF $\alpha$ ($p < 0.05$), demonstrating that neurons actively participate in the induction and / or maintenance of the CNS immune response, a finding of great importance that will change the image of the neuron as an active participant in infections of the central nervous system.
Pathological progression of genetic Creutzfeldt-Jakob disease with a PrP V180I mutation

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Introduction In comparison to sporadic Creutzfeld-Jakob disease (sCJD) with MM1-type and MM2-cortical (MM2C)-type, genetic CJD with a prion protein gene V180I mutation (V180I gCJD) is clinically characterized by onset at an older age, slower progress, and the absence of visual disturbances or cerebellar symptoms. In terms of pathological characteristics, gliosis and neuronal loss are generally milder in degree, and characteristic spongiform change can be observed at both the early and advanced stages. However, little is known on the progress of spongiform change over time or its mechanisms. Methods In this study, to elucidate the pathological course of V180I gCJD, statistical analysis of the size and dispersion of the major diameters of vacuoles in six V180I gCJD cases was performed, with five MM1-type sCJD and MM2C-type sCJD cases as controls. Results As a result, V180I gCJD showed no significant difference in vacuolar diameter regardless of disease duration. In addition, the dispersion of the major diameters of vacuoles in V180I gCJD was larger than that in the MM1-type, which was smaller than that in the MM2C-type. Conclusion We speculated that the absence of difference in the size of the vacuoles regardless of disease duration suggests that tissue rarefaction does not result from the expansion of vacuole size and increase in number of vacuoles in V180Ig CJD. These features were considered to be significant pathological findings of V180I gCJD.
Background: Gerstmann-Straussler-Scheinker syndrome (GSS) is well known as one of the hereditary prion disease. However, GSS is one of the rare disease, while not only clinical features but also neuropathological findings are still obscure. We have a chance to examine seven cases of GSS in our hospital group. We investigated these cases and made a special reference about them. Objective: To clarify the relationship between clinical feature and neuropathological findings of GSS. Methods: We examined genetically confirmed each GSS cases, whose mutation cites were P 102L; five cases, P 105L; one case, and G 217A; one case. Clinical features and neuropathological findings were investigated by conventional means. Results: Most popular point mutation of GSS was P 102L in Japan. Our result was same. In P 102L mutation cases, onset of age was around 50yrs, duration of illness was around 10yrs. Course of illness was slowly progressive phase about 5 yeares, and then, rapidly progression to apallic state for another 5 years. Initial symptoms were personality change or ataxic gait. In neuropathological examination, cerebellar degeneration, plaque were common findings, however, cerebral lesion, brainstem lesion and spinal lesion were different in case by case. Level of spongiosis was revealed slight to severe. Conclusions: Pathological change of cerebellum and plaques were common in GSS, however, divergent clinical feature and divergent neuropathological findings in our cases.
Leptomeningeal inflammatory aneurysm associated with leptomeningitis by tuberculosis. Exceptional finding in a postmortem case of systemic tuberculosis


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BACKGROUND Intracranial infectious aneurysms can be caused by bacterial, fungal, or viral organisms, the vast majority result from bacterial infections. Infectious aneurysms associated to leptomeningeal tuberculosis are very uncommon. We had an extensive review of literature and we found reported six cases. CLINIC CASE A twenty-eight-year-old man with medical history of annal abscess since one month before. The final event started two months before death with headache, agitation and unconsciousness; he entered to Hospital. At physical exploration, he had Glasgow 7/15, painful stimulation was present and decreased muscular strength. CT reported cerebral edema. Neurosurgery service realized a ventriculostomy and started antifimic treatment. He continued with neurologic deterioration and death. AUTOPSY FINDINGS We found systemic tuberculosis with miliar affection pattern in lungs, diaphragm, liver and spleen. The annal abscess was resolved. There was an extensive leptomeningeal tuberculosis and a thalamic tuberculoma. On microscopy, there was an extensive meningovasculitis, arterial cerebral arteries were merged, and anterior cerebral artery had wall inflammation, elastic layer was ruptured and lumen was dilatated due to infectious pseudoaneurysm. We detected acid-alcohol-resistant bacilli with Ziehl-Neelsen stain. CONCLUSIONS In our experience, we had 24 autopsy cases of leptomeningeal tuberculosis in 2000-2017 period; but we think than the evidence of pseudoaneurysm due to tuberculosis is exceptional; furthermore, only six cases of tuberculous pseudoanerysm were informed in central nervous system.
18F-THK5351 PET findings in familial Creutzfeldt-Jakob disease with V180I mutation: a clinicopathological study

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Introduction: THK5351 originally developed as tau tracer but our study of frozen brains confirmed binding to monoamine oxidase B, which is highly expressed in astroglia. Thus, THK5351 can be a good tracer to detect astrogliosis. Clinical summary: An 86-year-old Japanese woman presented with progressive insomnia and apathy for several months. Parkinsonism, cerebellar signs, and myoclonus were absent in entire clinical course. MRI showed hyperintensity of the cerebral cortex on diffusion-weighted images (DWI) and swelling in the cerebral cortex on T2-weighted images. Cerebrospinal fluid showed positive cut off value for tau and 14-3-3 protein, and RT-QUIC of prion protein (PrP) was positive. Analysis of PrP gene revealed V180I mutation with methionine/valine heterozygosity at codon 129. THK5351 PET images disclosed intense radioligand uptake in subcortical white matter regions, corresponding to DWI high signals. She died of hepatoma four months after the PET scan. Pathological findings: Neuropathological examination showed extensive spongiform changes with various-sized and non-confluent vacuoles in the cerebral neocortex. Neuronal loss is mild and immunostaining with 3F4 demonstrated very weak synaptic-type PrP deposition in the cerebral cortex. Western blot analysis of protease-resistant PrP showed a characteristic pattern with V180I CJD. The area of high uptake of THK5351 corresponded to astrogliosis without depiction of tau. Conclusion: This case confirmed that THK5351 could decorate astrogliosis and be employed to detect neurodegeneration, irrespective of tauopathy.
First autopsy proven case of VPSPr: Variably protease-sensitive prionopathy in Japan

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Introduction: Variably protease-sensitive prionopathy: VPSPr is a newly described human prion disease in the spectrum of Creutzfeldt-Jakob disease: CJD in 2008. In UK and USA cohort study in 2013, only 5 cases of VPSPr have been identified (prospectively and retrospectively) in UK, indicating VPSPr as a rare phenotype. Biochemical investigation characterizes that VPSPr shows detectable protease-sensitive fragments. Some investigators reported that molecular overlaps can be found between usual protease-resistant prionopathy and VPSPr in sporadic CJD. Clinical summary: 81 y-o women admitted to our hospital asked from GP, because of her memory disorder, rt-sided dysesthesia, and high intensity ribbon-like appearance in some cortices in DWI. At that time, she had several test: MMSE: 23 points, FAB: 6/30 points, CSF-QUIC: negative, PSD on EEG: negative. Six months later, she hanged around and admitted into care center, but still she could eat. She died of pneumonia after 3.5 years from disease onset. Pathological findings and immunoblot for anti-prion protein: Brain weight: 1186g, Macroscopic findings: Generally mild atrophy, but severe in the temporal pole. Histological findings: Neuronal loss and vacuolation were diffusely detected in the cerebral cortex and the basal ganglia with anti-prion antibody immunostaining (3F4). Mild neurofibrillary tangles, senile plaques and grains were also detected in the cerebral cortices. In immunoblot, variably protease-sensitivity was detected as VPSPr. Conclusion: The first case of sporadic CJD is reported as autopsy and immunochemical detected VPSPr in Japan.
An autopsy case of progressive multifocal leukoencephalopathy associated with idiopathic CD4 positive lymphocytopenia with a ten-year clinical course

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Introduction: Progressive multifocal leukoencephalopathy (PML) is a deadly demyelinating disease, caused by reactivation of the polyomavirus JC(JCV). PML associated with idiopathic CD4 positive lymphocytopenia (ICL) is rare and there are few reports of autopsy cases. Clinical summary: A 54-year-old man presented with dysarthria and gait disturbance. His symptoms deteriorated over months and he became akinetic mutism. FLAIR image of MRI showed high signal lesions in the pons and cerebellum, which extended to the cerebral white matter. PCR of CSF for JCV was positive and he was diagnosed with PML, although biopsy was not performed. Blood analyses revealed marked decrease in CD4 positive cell count. Serological tests for HIV were negative and there was no evidence of immunodeficiency, consistent with ICL. Cytarabine wasn't effective. 10 years after the onset, he died of cholangitis and postmortem examination was performed. Pathological findings: Severe loss of myelinated fibers was seen in the white matter of the cerebrum, brainstem and cerebellum. The white matter of the temporal lobe was partially spared. Typical findings of JCV infection were not observed, such as abnormal oligodendrocytes. Immunohistochemical analysis using anti-VP1 antibody was negative. PCR of the frozen section and formalin-fixed paraffin-embedded section for JCV were both positive. Conclusions: This is an extremely rare case of long-term survival of PML associated with ICL. Although there was no pathological evidence, the clinical presentation and results of PCR were consistent with PML. A long period of time may affect the pathological findings. This case may indicate that histopathological remission can occur in PML.
An autopsy case of MM2-Thalamic Creutzfeldt-Jakob disease

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A 39-year-old man admitted to the hospital with a two-year history of fatigue and anxiety, one-year history of insomnia, and four-month history of cognitive deterioration, diplopia, dysarthria and difficulty in walking for loss of balance. He was disoriented and disinhibited. Neurological examination revealed hyperreflexia, horizontal gaze-evoked nystagmus, internal strabismus and nasal voice. EEG and MRI were unremarkable. FDG-PET scans and Tc99m-ECD SPECT detected mild left thalamic hypometabolism. DAT-SPECT showed symmetrical reduction in bilateral putamen. CSF biomarker study revealed mild elevation of tau, but other biomarkers were not contributory, including phosphorylated tau, Aβ, 14-3-3 protein and RT-QUIC of prion protein. There was no response to donepezil, levodopa or steroid pulse therapy. The patient presented with progressive deterioration of mental state into akinetic mutism for a few months. At age 41, he died of respiratory arrest. Neuropathological examination revealed severe neuronal loss and gliosis in thalamus and inferior olivary nucleus, accompanying secondary tract degeneration, while other areas were relatively preserved. SNP at codon 129 of prion gene was Met/Met and western blot analysis detected faint band of type 2 prion protein. Neuropathological diagnosis was MM2T (thalamic form)- CJD. This case is unique in relatively young onset and secondary degeneration involving thalamic efferent fibers in addition to inferior cerebellar peduncle.
Clinical courses of patients with Creutzfeldt-Jakob disease in Shizuoka Institute of Epilepsy and Neurological Disorders, Japan

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Background & Objective: From 2002, we have diagnosed and cared forty-six Creutzfeldt-Jakob disease (CJD) patients in Shizuoka Institute of Epilepsy and Neurological Disorders (SIEND). Methods: 46 CJD patients presenting sequentially to SIEND between November 2003 and April 2018 were studied. Results: All patients were clinically diagnosed as probable CJD based on prion disease medical treatment guidelines in Japan. Initial symptoms were gait disturbance 13, speech disturbance 6, apathy 6, visual disturbance 4, limb palsy 4, agraphia 2, geographical disorientation 2, dizziness 2, involuntary movement 2 and others 5. Onsets were usually acute (25) or subacute (8), but 12 patients abruptly developed neurological symptoms within one day. Mean age of onset was 69.0 years old. Sex was male 19 and female 27. Mean disease duration from onset to death was 86 weeks. Sporadic CJD patients were 33 cases. Genetic CJD patients were 13 cases including eleven E200K and two V180I. 38 CJD patients were cared, and eventually 35 patients died in SIEND. Autopsy was performed in 14 patients. 13 neuropathological findings showed definite diagnosis of CJD. We reported CJD patients having specific neuropathological findings and clinical utility of brain SPECT. Conclusion: We reviewed 33 probable and 13 definite CJD patients. Abrupt onsets were frequently reported from family members. E200K mutations were very common in Genetic CJD patients. It is important to diagnose correctly and care CJD patients in central Shizuoka, Japan.
A 47-year-old male presented with progressive cognitive impairment, severe dysarthria, involuntary movements, urinary incontinence, and inability to ambulate without assistance. Two years earlier, he noted intermittent episodes of dizziness, imbalance, lightheadedness, and visual disturbances as well as rapid weight loss. Subsequently, he developed ataxia and dysarthria. On examination, he was alert, followed simple commands, but had severe dysarthria. His MoCA was 18/30. Extensive serological studies revealed no metabolic abnormalities, toxins, heavy metals, or infectious diseases. A paraneoplastic panel was unremarkable and genetic studies (complete ataxia panel, Fragile X) were negative. The cerebrospinal fluid revealed elevated protein, reduced A/T index (Aβ42/t-Tau), normal p-Tau, and negative 14-3-3 protein. A whole-body PET revealed no abnormalities and a head MRI showed mild white matter signal abnormalities. Diffuse but non-specific cerebral dysfunction was documented on EEG.

He died 5 years after the onset of symptoms. Neuropathological examination revealed marked brain atrophy and severe ventricular enlargement. The atrophy was particularly severe in the cerebral cortex, with almost complete loss of nerve cells, and severe astrogliosis. In the centrum semiovale, the axonal and myelin loss was severe. The basal ganglia, thalamus, amygdala, were markedly atrophic. Hippocampal atrophy was less prominent. There was also severe arteriolosclerosis. Immunoreactivity to PrP, with a synaptic pattern, was prominent in the cerebral and cerebellar cortices. The white matter degeneration in panencephalopathic Creutzfeldt-Jakob disease is generally considered to be secondary to the neuronal loss and the relatively long clinical course. A possible role of an associated severe small vessel disease has been rarely evaluated.
Coexistence of PrP and tau amyloids associated with the PRNP Q160X nonsense mutation

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Cognitive and behavioral changes, similar to those seen in Alzheimer disease (AD) may be associated with nonsense (stop codon) mutations in PRNP. A 31-year-old male was diagnosed as having an orbitofrontal syndrome, peripheral neuropathy, and a gastrointestinal disorder. Individuals in three generations of the family had suffered from presenile dementia. The patient's condition deteriorated rapidly and he died at 33 years of age. An autopsy limited to the CNS was carried out. The brain weighed 1,055 grams. Atrophy was severe in the frontal and temporal lobes, amygdala, hippocampus, corpus callosum, and the hemispheric white matter. The occipital horns of the lateral ventricles were severely enlarged. Histologic preparations with Luxol Fast Blue/Hematoxylin & Eosin revealed eosinophilic deposits in the cerebral and cerebellar parenchyma, often associated with the vasculature. For immunohistochemical analysis, antibodies to prion protein (PrP), tau, GFAP, alpha-synuclein, AIF1/IBA1, and calbindin were used. Cerebral and cerebellar cortices, subcortical nuclei, spinal cord, and the posterior nerve roots contained PrP-immunoreactive plaques as well as extensive deposits in the vessel walls. Thioflavin S highlighted the PrP deposits. The PrP angiopathy involved arterioles and capillaries. With the exception of the cerebellum, there was also a severe tau pathology, that mirrored that of the PrP deposits in the cerebral cortex and basal ganglia. DNA, extracted from brain tissue, revealed the PRNP Q160X stop codon mutation, which causes deposition of amyloid made of truncated PrP. The pathogenesis of tau pathology associated with truncated PrP requires further investigation.
Sensory nervous system involvement in a footpad-inoculated, Japanese encephalitis mouse model

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\textit{Introduction}: Japanese encephalitis (JE) remains the most important cause of mosquito-borne viral encephalitis. Based on the clinical observation that there is early and severe involvement of the thalami, we hypothesize that JE virus (JEV) could use peripheral sensory nerves and sensory pathways to enter the CNS following a mosquito bite. We investigated this using a footpad-inoculated, JE mouse model.

\textit{Methods}: Groups of 2-week-old ICR mice were inoculated in the left hindlimb footpad with JEV (Nakayama strain; $10^6$CCID$_{50}$/ml, volume 20µl). Tissues from sacrificed animals were collected on days 1 through 5 for histopathological analysis (n=6) and viral titration (n=6). Viral antigens and viral RNA were detected using specific immunohistochemistry and \textit{in situ} hybridization, respectively.

\textit{Results}: Viral antigens/RNA were focally detected in neurons of the thalamus contralateral to injected side (n = 4/6) at 3 days post-infection (dpi) and in the ipsilateral posterior horn of the spinal cord at 4 dpi. Dorsal root ganglia (DRG) and peripheral nerves were also positive for viral antigens/RNA. After 3 dpi, viral antigens/RNA could also be detected in other parts of the CNS, including cerebral cortex, brainstem, cerebellum and hippocampus. Virus could be cultured from the CNS starting 3 to 4 dpi but low viremia was cleared by 5dpi.

\textit{Conclusion}: Early infection of the thalamus, peripheral nerves and DRG in this mouse model suggests that JEV could use sensory nerves/pathways for neuroinvasion following introduction into the skin after a bite from an infected mosquito.
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An orally-infected hamster model for Coxsackievirus A16 infection confirms neurovirulence

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Introduction: Coxsackievirus A16 (CV-A16) is a common orally-transmitted, enterovirus that usually causes self-limiting, hand-foot-mouth disease (HFMD). Rarely, it has been reported that CV-A16 may cause severe neurological complications but this has not been adequately shown in human studies. Neither is there a good small, orally-infected animal model available for study. We developed a consistent, orally-infected CV-A16 hamster model to investigate HFMD associated with CNS infection.

Methods: Groups of 7-day old hamsters were orally inoculated with 100 μl (dose 1.12 x 10⁵ CCID₅₀/ml) of a CV-A16 mouse adapted virus strain, and observed for signs of infection. The tissues from infected hamsters were studied by light microscopy, immunohistochemistry and in situ hybridization to detect viral antigens and RNA, respectively. Tissues were also obtained for viral titration.

Results: All hamsters were infected and exhibited signs of infection such as ruffled fur, limb weakness, and paralysis, and were moribund or dead by 3-4 days-post infection. Viral antigens/RNA were detected in squamous epithelia in the oral cavity, paw and skin, and in the CNS. Neurons in the brain stem and spinal cord were mainly infected with no apparent involvement of the cerebral cortex, hippocampus and cerebellum dentate nucleus. Viral antigens/RNA were also detected in skeletal muscles and brown fat. Positive viral culture confirmed viral replication in the CNS.

Conclusion: The findings in this unique model confirmed that CV-A16 is neuronotropic. The distribution of squamous lesions is reminiscent of HFMD. This model is potentially useful for neuropathogenesis studies, and for anti-viral drugs and vaccine testing.
A Japanese encephalitis virus quasispecies with an E gene mutation exhibits reduced neurovirulence

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Introduction: Japanese Encephalitis virus (JEV) is the leading cause of viral encephalitis. Since viral genome mutations could potentially affect phenotype, we investigated E gene mutations in a JEV quasispecies to determine its neurovirulence.

Methods: A quasispecies (JEV-M) purified from a clinical isolate, was sequenced and E gene mutations were found. The phenotype of JEV-M was tested on human neuroepithelioma (SK-N-MC) and murine neuroblastoma (NIE-115) cells, and in a mouse model. Infectious clones harboring these mutations were generated from a published JEV clone (Muar-FLC), and phenotypically characterized to confirm the findings.

Results: JEV-M showed significant reduced infectivity in SK-N-MC and NIE-115 cells from 24 hour post infection (hpi) to 96 hpi. In the mouse model infected via footpad, 50%, 75% and 100% survival rates were observed in groups of animals infected with 20µL of \(10^6\), \(10^5\) and \(10^4\) CCID\(_{50}\)/ml of virus, respectively. Viral antigens/RNA in the cerebral cortex, hippocampus, thalamus, medulla and spinal cord were detected in the sick but not in surviving animals. The two E gene mutations (Y59H and A327T) identified in JEV-M were successfully incorporated in infectious clones, and tested to confirm the phenotype. The Y59H mutant clone showed a similar phenotype to JEV-M.

Conclusion: E gene mutations in the JEV genome could cause a reduction in neurovirulence both \textit{in vitro} and \textit{in vivo}. 
Trophic Factors Involved In Developmental and Adult Hippocampal Neurogenesis In Humans

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Introduction: We have previously described progenitor subtypes, their neurogenic potential and neuronal layer establishment in the hippocampal pyramidal layer and dentate gyrus in human fetuses and healthy and alzheimer's disease adults. Here, we assessed the expression of VEGF-A, VEGF-C, VEGFR2, VEGFR3 and TRKB in the developing and adult human hippocampus and characterized their cellular localization.

Summary: At GW13, VEGFA, VEGF-C, VEGFR3 and TRKB were strongly expressed in radial glial cells (RGCs) of the hippocampal ventricular zone (VZ) and the dentate anlage (DA). From GW16, their expression started to decrease in RGCs of the VZ, although VEGFR3 and VEGF-C expression increased in vessels and in the RGCs of the DA. In parallel, VEGF-A and TRKB expression increased in pyramidal and granule neurons from GW25. The expression of VEGF-A in neurons, vessels and glial cells persisted in adulthood. VEGFR2 was only detected in vessels. Conclusions: These observations support experimental data suggesting that VEGFR3 and VEGF-C directly stimulate progenitors in the developing human hippocampus. We did not find evidences of the neurogenic potential of VEGFA as VEGFR2 was only detected in vessels. Supported by EU grant HEALTH-2011-2.2.2-2/Develage.
Fiber tract anomalies of the CNS: anatomical variants of the midline-crossing mode of the anterior commissure

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Introduction: Fiber tract anomalies are a rare CNS-malformation; some known anomalies are agenesis of corpus callosum, abnormal course of the pyramidal tract including uncrossed/partially crossed pyramidal tract, and supracallosal dorsal fiber tracts. Additionally, we have previously described an abnormal entrance of the posterior spinal nerve roots into the spinal cord, and a trapping of a small number of callosal fibers by a unilateral fornix. The latter is clinically non-significant, therefore a normal anatomical variant. We now recorded some variable midline-crossing modes of the anterior commissure in relation to the fornix and studied it statistically. Methods: Macroscopic observation of 90 brains (Female:Male=34:56) in a non-selected human autopsy series, all adults (median: 52yrs) and without any malformations. Results: The majority of examined cases showed an anterior commissure midline crossing anterior to the fornix by 68.9% (62 cases; F:M=22:40) and posterior to the fornix by 17.8% (16 cases; F:M=6:10). 12.2% (11cases; F:M=5:6) of the cases showed that the anterior commissure crosses anterior to the fornix on one side and posterior on another side. One particular case exhibited on one side only a part of the anterior commissure fibers looping around the fornix. Clinical correlations could not be established. Conclusion: The variable crossing mode of the anterior commissure in relation to the fornix is a normal anatomical variant.
Development of 3D neuropathology based on tissue clearing technique

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Optical sectioning with light-sheet microscopy in combination with recent advances in tissue-clearing techniques is one of the promising strategies toward three dimensional visualization of large human tissues. Recently, we have developed a rodent brain/body clearing and imaging method, termed CUBIC (clear, unobstructed brain/body imaging cocktails and computational analysis). Hydrophilic CUBIC cocktails significantly enhanced whole mouse brain clearing via effective delipidation and homogenizing mismatched RIs without signal loss from fluorescent proteins. Additionally, an aminoalcohol in CUBIC reagent displayed highly efficient decolorization of the PFA-fixed blood by the elution of heme chromophore from hemoglobin. Our CUBIC cocktails are also applicable to human tissue block. We will introduce potential availability of CUBIC-based 3D neuropathology.
Basic study on the development of simple cognition system and device of the non-learning and non-stress type in the Alzheimer's disease model mouse

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Introduction: The previous cognition system for mice is designed on the base that an individual can learn. We try to establish the simple cognition system and device for Alzheimer's disease (AD) mice that cannot have adequate cognition, being based only on daily-living movement without invasive maneuvers. Methods: We used Tg(APPswe)2576KhaTg(Prnp-MAPT*P301L)JNPL3HImc mice as AD mice and age-matched littermates as normal controls. We set food and water box as Food Zone (FZ) at the corner in the routine breeding cage. We analyzed two conditions that there was Toy as the apparatus of behavior restrictions (Toy condition) or not (no Toy condition). Under Toy condition, we placed Toy at the opposite direction to FZ in the cage: the space (equivalent to Nesting hole Zone: NZ) was naturally formed between cage wall and Toy. We studied only on daily-living movement without invasive maneuvers, and used modified-Smart3.0 software for behavior analyses, using Activity factor among mouse behaviors. The analysis time was only ten minutes. Results: Under no Toy, there was no difference between AD and normal mice. Under Toy, AD mice had significantly higher Activity in FZ (AD pattern), and reciprocally normal mice showed significantly higher Activity in NZ (Normal pattern). Neuropathologically, AD-pattern mice exhibited senile plaques:SPs and neurofibrillary tangles:NFTs, but Normal-pattern mice did not have SPs and NFTs. Our behavioral results corresponded to neuropathological results. Conclusion: We have succeeded to develop the new system and device that can easily distinguish the mice having AD pathology from normal mice in only ten minutes.
Longitudinal diffusion tensor imaging and neuropathology revealed nerve fiber alterations in hereditary microcephaly model mice

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Introduction: Autosomal recessive primary microcephaly-5 (MCPH5) is caused by the mutation of the abnormal spindle-like, microcephaly-associated (ASPM) gene. This study aimed to demonstrate a correlation between radiological and pathological analyses in evaluating postnatal brain development using MCPH5-model mice. Methods: In vivo MRI was conducted on ASPM ortholog (Aspm) knockout (KO) mice, at postnatal three weeks (P3W) and P10W. Morphological and diffusion tensor imaging (DTI) analyses were performed with MRI data. Complementary histopathological analyses of their brains were carried out at P5W and P13W. Results: In the MRI analysis, KO mice showed significantly smaller brain sizes and larger ventricles at P3W and P10W. DTI analysis revealed that the fractional anisotropy (FA) values in the KO mice were significantly lower than those in the control mice in both the cortex and white matter, at P3W and P10W. Developmental changes in the FA values from P3W to P10W were less remarkable in the KO mice especially in the cortex. In the neuropathological analysis, the ratios of the horizontal to the vertical neurites (horizontal ratio) were significantly higher in the cortex, with a remarkable increase according to maturation at P13W in the control mice. Transient decrease in myelin basic protein-positive ratio in the white matter was observed in the KO mice at P5W. Conclusion: Temporal FA changes were correlated with pathological findings such as abnormal neurite outgrowth, assessed by the horizontal ratio, which may be applicable for analyzing diseased human brain development.
Expression of transporters of glucose and fructose in epithelial cells of the choroid plexus and ependymal cells of human and mouse brains

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Introduction: Incidence of obesity and type 2 diabetes mellitus is increasing in parallel with an increase in dietary fructose intake, and recent studies suggest that these conditions are associated with cognitive decline and dementia. To clarify the molecular basis of the relationship between high sugar intake and brain dysfunction, we investigated the localization of glucose and fructose transporters in human and mouse brains. Methods: Human brain samples (n = 6) were obtained at autopsy from 3 patients without and 3 patients with neurological diseases. Expression of GLUT5, GLUT8, and SGLT2 were examined with immunohistochemistry. The study was approved by the institutional ethics committee of the Faculty of Medicine, Kagawa University. Brain tissues were obtained from 9- to 10-week-old male C3H/He mice for immunohistochemistry, immunoblotting, and RT-PCR. Results: Immunoreactivity of fructose transporters, GLUT5 and GLUT8, were observed in epithelial cells of the choroid plexus and ependymal cells. Immunoreactivity of GLUT8 were also observed in subependymal astrocytes and microglia. Immunoreactivity of SGLT2, a sodium glucose co-transporter mainly expressed on the apical side of epithelial cells of the renal proximal tubules, was detected in choroid plexus epithelial cells. Conclusion: These results suggest that choroid plexus epithelial cells have direct transport systems for fructose and glucose, through which intravascular fructose and glucose move into cerebrospinal fluid. These molecules may have some roles in the pathogenesis of cognitive decline and dementia in patients with metabolic syndrome.
Expression of CRYM in different rat organs during development and its decreased expression in degenerating pyramidal tracts in amyotrophic lateral sclerosis

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Introduction: Down-regulation of μ-crystallin (CRYM) in the hippocampi of patients with Alzheimer’s disease was revealed by microarray analyses of autopsied brains from the Japanese general population (the Hisayama study). CRYM reportedly has two functions: it is a key regulator of thyroid hormone transportation and a reductase of sulfur-containing cyclic ketimines. We examined the expression pattern of CRYM in the rat brain during development. As CRYM is reportedly expressed in the corticospinal tract (CST), we also investigated CRYM expression in human cases of amyotrophic lateral sclerosis (ALS).

Methods: CRYM expression in developing rat brains was examined by immunohistochemistry and immunoblotting. CRYM expression in human ALS brains was examined by immunohistochemistry. Results: In the rat brain, CRYM was expressed in the cerebral cortex, basal ganglia, hippocampus and CST in the early postnatal period. As postnatal development progressed, CRYM expression was restricted to large pyramidal neurons in layers V and VI of the cerebral cortex and pyramidal cells in the deep layer of CA1 in the hippocampus. In these regions, CRYM-positive and negative neurons were distributed in a mosaic pattern. In human ALS brains, we observed marked loss of CRYM in the CST, especially distally. Conclusion: CRYM may play roles in development of cortical and hippocampal pyramidal cells in the early postnatal period, and later performs cell-specific functions in selected neuronal populations. The expression patterns of CRYM may reflect interactions with T3 or ketimines. The results also indicate that CRYM can be used as a marker of axonal degeneration in the CST.
Rapid immunohistochemical staining using an electric stirring device is useful for intraoperative brain tumor diagnosis

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Introduction: Intraoperative diagnosis of brain tumors is crucial for the decision of surgical procedures and application of intraoperative chemotherapy. Recently, an electric stirring device for rapid immunohistochemical staining (R-IHC) has been developed and its application to the intraoperative diagnosis is highly expected. In the present study, we examined the utility of R-IHC using the device for intraoperative brain tumor diagnosis. Materials and methods: Frozen sections of 211 cases of brain tumor were used for R-IHC with the electric stirring device, Hist Tech® R-IHC® (Nakayama Co. Ltd.). The primary antibodies used were EMA, somatostatin receptor 2, S-100 protein, GFAP, IDH1 R132H, p53, cytokeratins, TTF-1, lymphoid markers, and Ki-67. Results: The mean time from receiving materials to getting results of R-IHC was about 30 minutes. The mean number of stains for each case was five. Most antibodies gave reliable results, but Ki-67 labeling on frozen sections was less than that on formalin-fixed paraffin-embedded (FFPE) sections. In particular, R-IHC was effective in the following tumor types: 1) the diagnosis and grading of infiltrating glioma, 2) the diagnosis of metastatic tumor and the speculation of the primary site, 3) the diagnosis of malignant lymphoma, and 4) the diagnosis of meningioma, schwannoma, and pituitary adenoma. Conclusion: In the present study, we confirmed the usefulness of R-IHC using electric stirring device, which gave satisfactory stainings mostly within acceptable short periods. It should, however, be kept in mind that some antibodies, such as Ki-67 may be less sensitive on frozen sections than FFPE sections.
Characterization of the seed Aβ oligomers in the brains of APP transgenic mice

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Introduction: Extracellular deposition of amyloid-β (Aβ) peptides is crucial to the pathogenesis of Alzheimer's disease (AD), in which the critical role of the seeding capacity of aggregated forms of Aβ has been implicated. It has been shown that intracerebral injection of brain-derived Aβ fractions can exogenously induce Aβ deposition in Aβ precursor protein (APP) transgenic (tg) mice, although the molecular characteristics of the Aβ species that act as seeds in vivo remains elusive.

Methods: The Tris-soluble fractions of the brains of APP tg mice were separated by size-exclusion chromatography using a Superdex 75 column, and the Aβ-positive peaks verified by ELISA were injected into the unilateral hippocampus of the 10-month-old APP tg mice. Four months later, the Aβ in the hippocampus of the injected side was examined by Aβ immunohistochemistry and compared with those in the contralateral side. Fractions of wild-type mice were examined as a control.

Results: Tris-soluble Aβ in the brains of APP tg mice were separated into three peaks at elution positions of >200 kDa, 50-60 kDa and 10-20 kDa. Intrahippocampal injection of the >200 kDa Aβ fraction induced a unique pattern of Aβ deposition within the specific layers and fiber tracts of the hippocampus, whereas the 50-60 kDa Aβ, as well as the >200 kDa fraction from the wild-type mice did not elicit of Aβ.

Conclusions: The high-molecular-weight soluble Aβ oligomers of >200 kDa derived from Aβ-laden brains represent the seed Aβ species that play critical roles in the propagation of Aβ pathology, possibly through conformational changes.
Development of bipolar charged hydrogel for neuronal tissue engineering

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Introduction: Central nervous system has limited regenerative capacity. Current treatment strategies for traumatic brain injury, stroke or neurodegenerative diseases are insufficient to recover the function. Tissue engineering, replacing tissue with cells and artificial scaffold, is expected to neuronal regeneration. Cell adhesion to scaffold is one of the most important factors for anchorage-dependent growth including neural cells. Surface charge and wettability on substrates are important factors that affect cell adhesion and differentiation. We present that bipolar charged polymer hydrogel serves as scaffold for maintenance and differentiation of neural stem cells (NSCs). Materials and Methods: Copolymer hydrogels composed of anionic AMPS monomer with sulfonic and cationic APTMA with trimethylammonium residue was prepared at different ratios (anion to cation ratios were 1 to 0, 5 to 1, 3 to 1, 1 to 1 and 1 to 3). NSCs were cultivated on these gels and evaluated cell adhesion and differentiation marker by real-time PCR and Western blotting. Results: NSCs efficiently attached to neutral and hydrophilic gel designated as P(AMPS-co-APTMA)-S1A1. NSCs survived and extended cell body on this gel. Furthermore, P(AMPS-co-APTMA)-S1A1 gel promoted to astrocytic differentiation of NSCs through Jak/Stat pathway and suppressed oligodendroglial differentiation through decreasing Olig2 expression. Conclusion: P(AMPS-co-APTMA)-S1A1 hydrogel has a potential to provide scaffold for maintenance of NSCs with differentiation to astrocytic cell lineage which may contribute to protect neuronal cells and repair the brain tissue.
The development of the prominent immunohistochemistry method for human cholinergic neurons

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Introduction: Cholinergic neurons as lower motor neurons, pedunculopontine nucleus (PPN), and nucleus basalis of Meynert (NBM) are so important for neurophysiology and neurodegenerative diseases as Parkinson disease (PD) and amyotrophic lateral sclerosis (ALS). However, there are no immunohistochemistry method for human cholinergic neurons that can withstand neuropathological evaluation. Therefore, we developed a new immunohistochemistry method for human cholinergic neurons. Methods: We adopted anti-ChAT (mouse IgG1, AMAb91129; CL3169) for a specific antibody, Target Retrieval Solution, Citrate pH 6 (Dako)/autoclaving for pretreatment, and Can Get Signal immunostain ® (TOYOBO) for a sensitizer in immunohistochemistry process. As sites to stain, we chose human sliced specimens including each spinal cord, PPN, and NBM of controls and patients with PD, ALS and amyotrophic lateral sclerosis/parkinsonism-dementia complex (Kii ALS/PDC). Results: We succeeded to stain human cholinergic neurons clearly with excellent signal to noise ratio in all investigated sites. Moreover, we confirmed the accumulation of phosphorylated α-synuclein in PPN of a patient with PD, and the loss of lower motor neurons in spinal cord of patients with Kii ALS/PDC by using this method. Conclusion: Our method is useful for neuropathological diagnosis and researches of neurodegenerative disorders.
The Future of ICDNS

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Knowledge wants to be free! This realization formed the starting point of an initiative that culminated in the submission of an article on the International Classification of Diseases of the Nervous System (ICDNS), which I organised in 2002 (1). Jim Lowe and I also launched a website, www.icdns.org, and a follow-up article in PLoS Medicine (2) was complemented by a letter from Richard Stallman (3), with whom I had corresponded about the 'free community' approach. Unfortunately, the ICDNS project got delayed. All spare time during my later London years was absorbed by an arguably even more important project on the ethics of human brain banking (4). It further became clear that the online format originally chosen for ICDNS was suboptimal. In addition, the original idea had been to do most work anonymously but named authorship is more motivating and name recognition also creates trust. Now that concepts have matured and technology has advanced, I would like to undertake a fresh effort to make ICDNS useful for the international community of neuropathologists. The idea has remained that open debate and democratic consensus can eliminate the limitations of closed-circle classifications. The revised format of an online text(book) that can be used freely for training purposes seems most promising. I am also and especially inviting colleagues from countries where our medical specialty still needs to be established, including Australasia, South America and Africa to get in touch via email (webmaster@icdns.org) or, more effective, community chat (https://icdns.ngrok.io). 1.LancetNeurology2002;1(6):340; 2.PLoSMedicine2004;1(2):e16; 3. PLoSMedicine2005;2(2):e47; 4.http://blogs.plos.org/speakingofmedicine/2011/12/21/ensuring-respect-for-the-donated-brains-of-children/
D-neuron pathology: New clue for neuropsychiatric research

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Introduction: Relationship between pathophysiology of mental disorders and trace amines, such as beta-phenylethylamine, or tyramine has long been described from early in 1970's. D-neuron (trace amine neuron) system was described by Jeager et al. in 1983 in rat central nervous system. The author specified human D-neuron system, and examined D-neuron neuropathology of neuropsychiatric illnesses to discover novel treatments. Methods: Immunohistochemistry by using antibodies against monoamine-synthesizing enzymes and postmortem brains of controls, patients with schizophrenia obtained by legal and pathological autopsy (registered cases of national hospital research resource network) were used. Available references were used to establish pathophysiological hypothesis. Results: I specified anatomical subgroups of mammalian D-neurons into 18 groups from D1 (spinal cord) to D18 (cerebral cortices) in a caudorostral order. D-neurons could not be detected in monkey striatum, whereas, D-neuron system was developed in human forebrain. In postmortem brains of patients with schizophrenia, D-neurons were reduced in D15 and D16 (Ikemoto et al., 2003). Newly established "D-cell hypothesis of schizophrenia" (Ikemoto, 2012, 2016), a pivotal theory to link neural stem cell dysfunction hypothesis to dopamine hypothesis, explained mesolimbic hyperdopaminergia and disease progression of schizophrenia (Kippin et al., 2005), showing a novel direction in medicinal chemistry, trace amine-associated receptor 1 (TAAR1) as a target receptor (Revel et al., 2013). Domestically developed SEP-363856, a TAAR1 partial agonist, was preceded to a phase 2 clinical trial in foreign countries. Conclusion: D-neuron pathology induces neuropsychiatric novel therapeutic strategies. The D-neuron might be available in future regenerative medicine using induced pluripotent stem cells (iPSC).
Maternal repeated cold stress alters morphology of noradrenergic neurons of offsprings: Immunohistochemical study using rat model

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It is important to know whether prenatal environment influence on the morphology of offspring central nervous system. Here the author shows the findings of an immunohistochemical study by using prenatal stress model of rats. The author and her colleagues examined the effect of maternal repeated cold stress (RCS) on the development of catecholamine neurons in offspring using 8-day-old offspring and tyrosine hydroxylase (TH) immunohistochemistry. RCS was loaded to pregnant rats between days 10 and 20 after fertilization. The frontal and cingulate cortices tended to contain fewer TH-immunoreactive (-ir) fibers, and the density of TH-ir varicosities with a large size (more than 7 μm in diameter) was significantly (p<0.05) less in rats prenatally exposed to RCS than controls. The locus coeruleus neurons of rat prenatally exposed to RCS displayed less TH immunoreactivity than controls. In the medullary C1/A1 catecholaminergic field, size of TH-ir neurons was smaller and the quantity of TH-ir fibers was less in prenatally exposed rats, although the difference was not significant. In the originating and projection fields of midbrain dopaminergic systems, we could not detect any differences in TH-ir structures between the two groups. These findings showed that prenatal RCS impaired development of catecholaminergic neurons, notably noradrenergic neurons of pups. The result is concordant with our clinical observations showing the efficacy of noradrenergic stimulants for patients with developmental disorders including attention deficit hyperactivity disorder (ADHD).
Differential Gene Expression Analysis in Pediatric Langerhans Cell Histiocytosis, A Comparison between CNS and Bone Lesions

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Introduction: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia with well-documented CNS and bone involvement. However, the underlying mechanisms that causes the lesion to be selectively expressed primarily as a CNS lesion or as a bone lesion has not been clearly elucidated. This study compared the difference between the upregulated and downregulated genes in the LCH of the brain versus the bone samples of pediatric patients to determine the difference in the gene expression. Methodology: Gene frequency counts from the whole exome sequence data of pediatric patients with LCH were analyzed. The frequency of expression were differentiated by analysis of the transcript reads to determine if there is a change in the upregulated and downregulated transcripts in the CNS LCH versus the bone LCH group. Results: CNS LCH patients exhibited an upregulation in the Dysbindin Domain Containing 1 (DBNDD1) gene versus matched controls that showed a downregulation of the said gene. In comparison, B Cell Associated Protein (BCAP29) and Pyruvate Dehydrogenase Kinase (PDK2) was upregulated in the CNS cases but was not expressed in the normal brain control. Oxysterol Binding Protein Like 7 (OSBPL7) is increased in both the brain and bone LCH cases but was not expressed in the normal brain control. Conclusion: Identification of unique gene expression in CNS versus bone LCH contributes to the understanding of the underlying mechanisms that may explain the difference in tumor behavior in different locations.