

Cerebral amyloid angiopathy initially occurs in the meningeal vessels

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To clarify the regional frequency of cerebral amyloid angiopathy (CAA), we counted sections of blood vessels showing positive staining for A β in the subarachnoid space (SAS) and cerebral cortex (CC) using paraffin-embedded sections of the frontal, temporal and occipital lobes. The specimens had been taken for routine neuropathological examination from the brains of 105 Japanese patients (aged 40-95 years) selected from among 200 consecutive patients autopsied at our hospital. We examined the anatomical ratios of blood-vessel sections in the SAS relative to the CC in 3 selected CAA cases, and those of A β -positive blood-vessel sections in CAA cases. CAA was found in 53 of the 105 cases. The anatomical ratio of blood-vessel sections in the SAS relative to the CC was 1/3.70-1/4.37 (mean: 1/3.94). The ordinary CAA group, in which CAA was seen in both the SAS and CC, included 41 cases (77.4%). In 37 of these cases, the SAS/CC ratio of A β -positive blood vessels was 1/0.05-1/0.66 (mean: 1/0.26), and in the other 4 cases the ratio was 1/1-1/1.5. In the ordinary CAA group, the SAS/CC ratio of A β -positive blood vessels was smaller than the anatomical ratio. The meningeal CAA group, in which CAA was found only in the SAS, included 12 cases (22.6%). These patients ranged in age from their fifties to their nineties. There was no case in which CAA was limited only to the CC. We concluded that CAA initially develops in the meningeal blood vessels, and not in the cortical blood vessels.

Iatrogenic Embolization Causing Stroke Following Cardiac Intervention

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Introduction: Iatrogenic cerebral embolization following cardiac investigative procedures may result from polymer sheaths of catheters (HPE), cardiac valve calcifications (CVC), and air embolism from open heart surgery. This retrospective clinical pathologic analysis was undertaken to ascertain the frequency and extent of this potentially fatal complication. **Methods:** This retrospective clinical pathologic autopsy analysis with pre-mortem diagnostic imaging correlation identified 110 individuals who had undergone endovascular procedures between 2010-2016 within 90 days of death followed by hospital autopsy. Clinical outcomes, radiologic studies and autopsy materials were reviewed. **Results:** Histologic evidence of HPE was found in 25% (25/102), 54% (26/48) showed evidence of infarction in post-procedural imaging, with radiologic evidence of infarction in 32% (8/25) of cases with HPE histology. The HPE-involved organs included: kidneys (n=13), lungs (n=8), heart (n=7), spleen (n=4), brain (n=2), liver (n=2), pancreas (n=2) and colon, stomach, adrenal gland and skeletal muscle. Endovascular aortic repair was associated with the greatest density/distribution of HPE. HPE material showed degradation with time and was often associated with an inflammatory response including multinucleated giant cells. HPE directly contributed to death in three cases. Six cases of calcified cerebral emboli complicated aortic valve procedures. One fatal air embolism followed open heart surgery, and one cardiac tissue embolus resulted in a major stroke. **Conclusions:** We advocate for greater awareness of these under-recognized and occasionally fatal complications of endovascular procedures. Targeted post-procedural imaging has a role in the identification of iatrogenic embolic infarcts.

Slow compression brain injury: clinical case and animal model

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Brain shows atrophy by slow compression. However, little is known about the neuropathological features of compressed tissue. We examined pathological changes of a brain with slow compression by meningioma, and developed an animal model of slow compression brain injury. Clinical case: An autopsied brain of 75 years old male with frontal meningioma was cut and three large coronal section brain specimens stained with Kluever-Barrera or Bodian method were made. Thickness of peri-tumoral gray matter was 0.33 ± 0.22 (m \pm SD) of the control. Cross sectional area of ipsilateral hemisphere was reduced to 0.77 ± 0.02 of the opposite side. Nuclear height/width ratio of neuron was significantly reduced in the peri-tumoral brain tissue to 0.48 ± 0.13 from the control. The reduction of height/width ratio was in parallel with the reduction of gray matter thickness. Animal model: A device for slow compression was installed on the parietal cortex of Japanese white rabbits (n=9) and gradually compressed ($100 \mu\text{m}/\text{day}$) for 56.0 ± 1.3 days. Cortical thickness decreased to 0.19 ± 0.07 of the control, cross sectional area decreased to 0.63 ± 0.10 of the control, Nuclear height / width ratio of the neuron decreased to 0.43 ± 0.10 from the control. Neurite density was decreased in Golgi staining specimens. Coiling of perforating artery was observed in the soft-X-ray angiography, but the regional cerebral blood flow measured by the hydrogen clearance method was kept at 0.95 ± 0.17 of the control. Conclusion: Slow brain compression causes no regional blood flow change, but tissue atrophy, neuronal deformation and reduction of neurite density.

Chronic traumatic encephalopathy: The role of gliovascular pathology

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Introduction: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder associated with repetitive mild traumatic brain injury (mTBI). Currently, CTE may only be diagnosed post-mortem, by examining the deposition of tau in both astrocytes and neurons around the cerebral microvasculature at the depths of sulci. The gliovascular unit (GVU) is known to be disrupted in the acute phase of traumatic brain injuries. Due to the proximity of the tau pathology to the vasculature in CTE, we investigated whether the GVU is also disrupted in individuals with CTE pathology. **Methods:** We studied the brains of 10 boxers, from the Corsellis archival collection, who were diagnosed with CTE according to modern diagnostic criteria. Using immunohistochemistry and tissue clearing (FASTClear), we have investigated tau pathology, blood-brain-barrier integrity, basement membrane composition and the morphology of the glial limitans. **Results:** We observed widespread disruption of multiple GVU components, with extravasation of blood-borne fibrinogen, as well as fibrinogen within astrocytes, some of which exhibited tau pathology. Disruption of the glial limitans was a common feature, manifest as retraction of astrocytic end-feet and a change in the composition of the basement membrane. These disruptions were also evident in areas where tau pathology was not present. **Conclusion:** CTE tau pathology is shown to be associated with several aspects of GVU disruption. In addition, the same pathology is seen independently of tau, indicating that GVU pathology may precede tau deposition. This may also indicate that GVU disruption may play a role in the underlying mechanism behind the development of CTE.

The neurodegeneration in old single episode head injury is not caused by Alzheimer pathology

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Introduction Increasing evidence suggests that traumatic brain injury (TBI) is linked to neurodegeneration later in life with increased incidence of Alzheimer disease (AD). Although chronic traumatic encephalopathy (CTE) is known to be linked with repetitive TBI, the association of single episode TBI with the neurodegeneration is not certain. We have recently shown that WNT pathway proteins (DKK1 and beta Catenin) are less altered in AD with TBI compared with AD without TBI. **Methods** We aim to investigate the distribution of Tau, beta A4, TDP43, alpha synuclein, ApoJ, DKK1, CD68 in brains from 19 patients (18-75 y) with severe cognitive decline after 1-22 years of a single episode TBI. **Results** All brains have significant traumatic axonal and vascular damage due to head injury. Three patients (75, 74, 56 y) showed Tau Braak stage IV, II, and I respectively. Two patients (50 and 41 y) showed localised CTE pathology stage one associated with high ApoJ. All brains are negative for DKK1, alpha synuclein, TDP43. **Conclusion** Neurodegeneration in old single episode TBI is caused by traumatic axonal and vascular injuries but it is unlikely due to pathology (AD or CTE).

Sequential evaluation of pathological changes following spinal cord injury in a canine model

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The purpose of this study was to evaluate the histological findings following induced spinal cord injury in dogs < 2 days and < 2 weeks post-injury. Eight dogs were included, and spinal cord injury was induced using an epidural balloon catheter. Two dogs were sacrificed at each of four time points: immediately after the procedure, day 1 after the procedure, and at 1- and 2 weeks after the procedure. Over the 2 weeks, haemorrhage at the primary injury site expanded quickly, then decreased in size, but spongiform change, parenchymal necroses, and gliosis remained. Rostral and caudal to the primary injury site, haemorrhage, haematoma, and similar changes occurred indicating ascending and descending haemorrhage post-injury, which resolved over time. Changes were seen in both the gray and white matter. This is the first report to clarify the sequential evaluation of pathological changes following spinal cord injury in dogs.

Novel control mechanism of H3K27me3 by mTOR complexes

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Introduction: GBM (glioblastoma) is the most common and deadly human primary brain tumor and it is urgent to reveal the detailed mechanism related to pathological conditions in GBM cell. In recent years, epigenetics has been reported to be important in many types of cancers, but the key factors which cause epigenetic changes in cancer remain to be clarified. **Methods:** We used the human GBM cell line U87 with active EGFR mutation (EGFRvIII) as a GBM model and investigated the factors which control epigenetics. **Results:** In human glioblastoma tissues and cell lines, high expression of tri-methylated lysine at 27 on Histone H3 (H3K27me3) was observed in tumors with EGFRvIII in comparison with those with wildtype EGFR. H3K27me3 has been known as the important epigenetic mark to regulate various genes by remodeling the chromatin structures. We investigated the detailed mechanism to regulate H3K27me3 downstream of EGFR and found that mTORC1 increases the translation of H3K27-specific methyltransferase EZH2, and mTORC2 promotes H3K27me3 by controlling the production of methylation donor substrate SAM (S-adenosylmethionine). **Conclusion:** Downstream of EGFR signaling, H3K27me3 is cooperatively controlled by two mTOR complexes. This mechanism is expected to be a new therapeutic target against cancer cell.

Comparison of the Gene Expression in Gliosarcoma versus Glioblastoma and Other Astrocytoma Variants

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Introduction: Gliosarcoma (GS) is a very rare primary mixed tumor of the CNS, which presents with a biphasic pattern of glial and malignant mesenchymal elements. In contrast, glioblastoma multiforme (GBM) is a malignant primary brain tumor with astrocytic differentiation that comprise as much as 60% of astrocytic neoplasms. The aim of this study is to show the difference in the mutated genes and the copy number alteration expressed in Gliosarcoma versus in GBM using the data provided by The AACR Project GENIE Consortium, under the AACR Project GENIE: Powering Precision Medicine Through An International Consortium, in preparation. **Methods:** The difference in the mutated genes and copy number alteration between GS and other groups of astrocytoma is analyzed to establish a targetable gene among these groups for therapeutic purposes. **Results:** There is a difference in the frequency of gene expression of the same mutated genes between GS and GBM as well as between GS and the other astrocytoma variants ($p > 0.00001$), but not between GBM and anaplastic astrocytoma, the WHO grade II astrocytoma. The number of accumulated gene mutations in each classification also significantly differs. **Conclusion:** Information on the difference in the mutated gene expression of GS versus GBM allows for future evaluation of genes that may serve as potential therapeutic targets in GS that is distinct from GBM.

Expression of GPR17, a negative regulator of oligodendrocyte differentiation and maturation, in Nasu-Hakola disease brains

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The G protein-coupled receptor 17 (GPR17), a Gi-coupled GPCR, acts as an intrinsic timer of oligodendrocyte differentiation and myelination. The expression of GPR17 is upregulated during differentiation of NG2⁺ preoligodendrocytes into O4⁺ premyelinating oligodendrocytes, whereas it is markedly downregulated during terminal maturation of myelinating oligodendrocytes. Nasu-Hakola disease (NHD) is a rare autosomal recessive disorder caused by a loss-of-function mutation of either TYROBP (DAP12) or TREM2. Pathologically, the brains of NHD patients exhibit extensive demyelination designated leukoencephalopathy, astrogliosis, accumulation of axonal spheroids, and activation of microglia predominantly in the white matter of frontal and temporal lobes. Although GPR17 is a key regulator of oligodendrogenesis, a pathological role of GPR17 in NHD brains with relevance to development of leukoencephalopathy remains unknown. We studied the expression of GPR17 in five NHD brains and eight control brains by immunohistochemistry. We identified GPR17-immunoreactive premyelinating oligodendrocytes with a multipolar ramified morphology distributed in the white matter and the grey matter of all cases examined. However, we did not find statistically significant differences in the number of GPR17-expressing cells between NHD and control brains both in the white matter and the grey matter due to great variability from case to case. These observations do not support the view that GPR17-positive premyelinating oligodendrocytes play a central role in the development of leukoencephalopathy in NHD brains.

Neuropathology of SOD1- linked familial ALS with marked intrafamilial phenotypic variation

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Introduction: Familial ALS with a mutation in the superoxide dismutase (SOD1) gene often shows marked intrafamilial phenotypic variation, although its pathologic background remains to be investigated. **Methods:** Immunohisto- and immunochemical studies using the SOD1 oligomer antibody were performed on postmortem brain and spinal cord from three patients (two brothers and a son) with C111Y mutation in SOD1 gene. The patients came from a family in which the rate of progression of the illness varied markedly over three generations. Two of them (father and son) presented with an ALS phenotype and both died at age 53, 1.2 and 4 years after the onset. One patient with a spinal muscular atrophy (SMA) phenotype died at age of 89 more than 50 years after the onset of his disease. **Results:** The severity and the distribution of the lesions are different among patients, reflecting their clinical features. Loss of lower motor neurons was demonstrable in all patients, although only by quantitatively in the patient with SMA phenotype with the longest survival. Pathological oligomers could be detected immunohistochemically in all patients and immunochemically in the anterior horn of frozen tissues in two patients including SMA phenotype. **Conclusions:** Despite the marked phenotypic difference, pathological oligomers could be found in all patients immunohisto- and/or immunochemically, suggesting the presence of acquired factor(s) to modify SOD1 misfolding processes.

Excessive soluble iron stimulates microglia to release glutamate in ALS spinal cords

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Introduction: Previous studies have demonstrated increased iron and glutamate levels in the spinal cord of amyotrophic lateral sclerosis (ALS). The present study aimed to clarify the relationship between these two substances. **Methods:** Immunohistochemical and immunoblot analyses were carried out on spinal cords at autopsy from 10 sporadic ALS patients and 10 age-matched control subjects. A mouse microglial cell line (BV-2) was used for cell culture experiments. **Results:** Ferritin (Ft), aconitase 1 (ACO1), TNF α -converting enzyme (TACE), and glutaminase C (GAC) were mainly expressed in ALS activated microglia. Total protein-normalized intracellular soluble iron content and β -actin-normalized Ft optical density on immunoblots were significantly increased in the ALS group as compared to the control group. Ferroportin (FPN) expression levels were significantly reduced in the ALS groups as compared to the control group. Ferric ammonium citrate (FAC) let BV-2 cells increase intracellular soluble iron content and Ft expression levels. FAC also let BV-2 cells release glutamate and TNF α , and these increases were cancelled by pretreatment with inhibitors for ACO1 and TACE, respectively. TNF α let BV-2 cells release glutamate, and the increase was cancelled by pretreatment with GAC inhibitor. The TNF α -released hepcidin let BV-2 cells reduce intracellular FRP expression levels. **Conclusion:** Our results provide in vivo and in vitro evidence that increased soluble iron levels stimulate microglia to release glutamate in ALS spinal cords via ACO1, TACE and GAC. Additionally, it is likely that a mechanism by which intracellular soluble iron levels are maintained in microglia may be underlined in ALS.

Stereoscopic inspection of autopsied brain reconstructed from two-dimensional images

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Introduction:Macroscopic inspection of autopsied brain constitutes a connection between clinical manifestations and microscopic findings. Clinical image such as CT and MRI are 3-dimensionalized, while macroscopic counterpart of the autopsy brains are usually presented on 2 dimensional basis. This is the first trial to overcome this gap by creating a 3-dimensional surface model of autopsied brains. **Materials and methods:**Cerebral hemispheres from five autopsied brains (normal, progressive supranuclear palsy, dementia with Lewy bodies, amyotrophic lateral sclerosis and Alzheimer disease), routinely fixed in formalin were photographed from multiple directions at about 30 degrees intervals using digital single-lens reflex camera. These 2-dimensional images were put into a software Autodesk ReCap Pro cloud service(<http://www.autodesk.co.jp/products/recap/overview>) to reconstruct a 3-dimensional surface model. **Result:**Reconstruction of 3-dimensional surface model of the brain hemisphere was successful from 60 to 80 images. It is now possible to observe gross or regional atrophy at whatever scale from whatever magnifications, and detect characteristic findings of disease. **Conclusion:**This is the first report that successfully established a 3-dimensional surface model reconstruction method of human autopsied brains. There is still room for improvement regarding standardizing image acquisition (lighting, angle, stabilization of the whole brain) and data processing. By using this 3-dimensional overview, it is now possible to more accurately identify the relationship between the brain surface and microscopic findings and clinical findings including imagery. Furthermore, these reconstructed datasets may be useful for quantification of atrophy that may represent disease-specific patterns.

Hippocampal adult neurogenesis is perturbed in microcephaly model mice with aging

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Introduction: Autosomal recessive primary microcephaly-5 (MCPH5) in human is caused by the mutation of the abnormal spindle-like, microcephaly-associated (ASPM) gene. The aim of our study is to elucidate the role of ASPM in the hippocampal adult neurogenesis with aging by immunohistochemistry and morphometry. **Methods:** We prepared CAG-mediated Cre-loxP conditional ASPM ortholog (*Aspm*) knockout (KO) and WT mice of both sexes at postnatal 10-20 weeks, 40-50 weeks, 60-70 weeks and 100-110 weeks. Mice received six bolus administration of BrdU (50 mg/kg; i.p.) every 12 hours and were sacrificed 24 hours after the last injection. Fixed brains were embedded in paraffin and immunostained for BrdU as well as neuronal lineage markers, such as doublecortin and nestin. We evaluated the hippocampal volume and the number of BrdU-, doublecortin- and nestin-positive cells in the dentate gyrus of the hippocampus in both genotypes and sexes. **Results:** Total volume of hippocampus and dentate gyrus was significantly smaller in *Aspm* KO mice compared to WT mice at any age, although there was no tendency of age-dependent reduction in volume. The number of BrdU-positive cells in the dentate gyrus showed a decrease with age in both genotypes; however, the reduction was significant in *Aspm* KO mice as compared to WT mice at any age. **Conclusion:** These data suggested that *Aspm* might contribute to the proliferation of hippocampal new-born cells in adult mice, although further investigation is needed to verify molecular pathomechanisms.

Presumptive function of microcephaly related gene *Aspm* during murine brain development

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Introduction: The mutation of *ASPM* (abnormal spindle-like microcephaly associated) causes primary autosomal recessive microcephaly in human. In order to evaluate the pathomechanisms of abnormal brain development, we performed histometric analyses using mice model.

Methods: Brain specific *Aspm* knockout mice (*NesCre;Aspm^{ff}, Aspm cKO*) were generated and the phenotype of the embryonic brains was examined. The brains were removed at embryonic day 12.5 (E12.5), E14.5 and E16.5, fixed with 4% PFA and the cryosections were stained with the following primary antibodies and labeling kit.; Tbr1, Ctip2 and Satb2 (for studying layer formation), pHH3, BrdU and EdU (for analyzing proliferation), CC3 and TUNEL (for detecting apoptosis). For neurogenesis, birthdating analysis using EdU was conducted. The brains were collected 2 days after EdU administration into pregnant mice (E12.5 or E14.5). The images were obtained with confocal laser microscope and analyzed using ImageJ.

Results: A deficiency of *Aspm* resulted in a reduction of cerebral wall thickness at a late neurogenesis (E16.5) during murine corticogenesis. Proliferation index evaluated by pHH3 and BrdU labeling did not show apparent changes at all stages analyzed. Neurogenesis index examined by EdU labeling reduced only at the later stage (E16.5). In contrast, a significant increase in apoptosis was found in the cerebral wall of *Aspm cKO* from early stage (E12.5) to late stage (E16.5) of neurogenesis.

Conclusion: Our findings suggested that a high occurrence rate of apoptosis during corticogenesis might be one of the underlying mechanisms of microcephaly due to deficiency of *Aspm*.

Epoch-making therapy that delays ALS progression in G1H-G93A ALS mice: oral administration of non-purine-analogue xanthine oxidoreductase inhibitors (XORIs)

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Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disease. The only universal drug currently available to treat ALS is the glutamate antagonist riluzole. **Methods:** With respect to three non-purine-analogue (np)-XORIs, we used TEI-6720 (Febuxostat), Y-700 and FXY-051 (Topiroxostat), and purine-analogue Allopurinol was also used. As a placebo, methylcellulose (drug solvent) was given. We orally administered four XORIs and placebo to G1H-G93A mice carrying human mutant G93A-SOD1 (25 copies) or littermates. As for clinical evaluation, XORIs and placebo were administered at following two points: 80 days of age (preclinical stage) and at the ALS onset. The five exercise testing was conducted: extension reflex, inclined plane, footprint, rotarod, and beam balance tests. Concerning neuropathological studies, XORIs and placebo were administered from 80 to 115 days of age to G1H-G93A mice or littermates. **Results:** All np-XORIs significantly delayed disease onset, prolonged survival and the duration of disease stages, improved ALS symptoms, and alleviated weight loss. All exercise testing showed the significantly-improved motor function in G1H-G93A mice treated with np-XORIs. Significant amelioration of disease was seen even when np-XORIs were administered after the ALS onset. Histopathological quantitative evaluation at 115 days revealed that G1H-G93A mice treated with np-XORIs had well-preserved motor neurons and fewer inclusion bodies, compared with mice treated with Allopurinol or placebo. Regarding clinical and pathological results, Allopurinol was the same as placebo. **Conclusion:** Our results indicate that np-XORIs could apply to oral therapy of human ALS patients.

Spectrum of central nervous system tumors in infants according to 2016 WHO Classification from a tertiary care centre in India

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Introduction: Central Nervous System (CNS) tumors in infants (< 3 years-of-age) are rare and form a distinct subset of pediatric CNS tumors. These tumors differ from tumors in older children with respect to clinical profile, histology, management and tend to have poorer outcome. **Objectives:** a) To analyze the spectrum of all CNS tumors diagnosed in infants; b) To recategorize them according to 2016 WHO classification, wherever possible; c) Compare the statistics with the available literature. **Methods:** All cases diagnosed over the last 14 years (2002-2016) were retrieved from the archives of Department of Pathology, AIIMS, New Delhi. **Results:** A total of 378 cases were identified (2.7% of total CNS tumors). The tumors were equally distributed across supratentorial and infratentorial compartments followed by spinal cord. Nearly 38% tumors were diagnosed in infants < 1 year-of-age. Male preponderance (M:F=2.2:1) was noted. Almost one-fourth were astrocytic tumors comprising mainly of Grade I pilocytic astrocytomas (62%). Glioblastomas (17%) and Grade II/III diffuse astrocytomas (17%) were less common. Embryonal tumors (13.5%) (Medulloblastoma-36, AT/RT-9, ETMR-2, NOS-4), ependymomas (8.7%) (Grade III-24, Grade II-9), germ-cell-tumors (5%), craniopharyngiomas (4%), choroid plexus tumors (3.2%), meningiomas (3.2%), schwannomas (3%), glioneuronal (2.3%), and few cases each of hemangioblastoma, lymphoma, pineoblastoma and oligodendroglioma were seen. Among malignant tumors, medulloblastoma were the most-common, followed by anaplastic ependymomas and glioblastomas. **Conclusions:** The spectrum of infantile brain-tumors in our institution is largely similar to world-wide data with astrocytomas being the most common. However, one study published from South-India found choroid plexus tumors, while another from the far-east found medulloblastomas to be the most-common. Larger multi-institutional studies are warranted to analyse racial and molecular differences from their childhood and adult counterparts.

Unusually high frequency of dual/ double pathology in neurocysticercosis causing drug resistant epilepsy in India. Chance association or causal?

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Introduction: Neurocysticercosis(NCC) as cause of drug resistant epilepsy(DRE) is more commonly reported from India (0.06%). We review the neuropathological findings in patients undergoing resective surgery for DRE due to NCC. **Methods:** Histologically confirmed cases of NCC causing DRE in patients undergoing resective surgeries between 2004-2018 in NIMHANS, India were collected. Clinical, demographic and neuropathological findings were reviewed. Histological alterations in adjacent tissues were evaluated using NeuN, GFAP, phosphorylated neurofilament, vimentin, CD34 for glial/neuronal alterations and Masson trichrome, and Luxol Fast blue for evidence of fibrosis/demyelination to determine cause of epileptogenesis of these lesions. **Results:** There were 13 cases of NCC causing DRE, constituting 0.037%[13/346]. [Age range:17-35yrs, Male:Female=1.1:1]. Seizure duration ranged from 3-20yrs, with seizure onset between 5-27yrs. On MRI, lesions were T1 hyperintense and T2 isointense with blooming on GRE, and CT showed calcification in 11/13. All had single cysticercal lesion and involved hippocampus(7/13), temporal(2/13), frontal(2/13), parietal(1/13), amygdala(1/13). On histopathology, cysts were degenerated(6/13) or fibrocalcific(7/13) stage. Adjacent cortex revealed fibrosis(9/13), inflammation(4/13), gliosis(4/13), axonal disruption/beading(2/13), and variable synaptic/neuronal dysmorphic changes. Vascularization was uncommon. Associated epileptogenic lesions were identified in 10/13 [76.9%], Hippocampal sclerosis(HS) Type 1(8/10), Focal cortical dysplasia(FCD) 1B(1/10), FCD 2B(1/10). Dentate gyrus revealed thinning, gaps or duplication(5/8). Surgical outcome available in 2 [Engel Ia and Ib]. **Conclusion:** Associated HS (Dual pathology) was common in majority (61.5%) suggesting that HS is a secondary/epiphenomenon. Perilesional changes such as inflammation, gliosis, dystrophic synaptic and axonal pathology play a role in inducing epilepsy. Association of FCD suggests that these may not always be developmental.

Using models of cell-cell interactions in the focal cortical dysplasia (FCD) to unravel the cellular diversity in developmental cortical lesions

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Introduction: Interactions between different cell types seem to be critical in developmental cortical lesions. However, methods to understand these interactions are limited. We have investigated cell-cell interactions in FCD, one of the most common cortical lesions leading to multidrug-resistance in paediatric epilepsy. We hypothesised that FCD contains multiple cell types and their interactions are important in explaining the pathogenesis. *Methods:* Using gene expression analysis, we identified the major secretory molecules in balloon cell cortical dysplasia (FCDIIb and cortical tubers). Then, we characterised the cell types expressing these signalling molecules using immunohistochemistry. Finally, to explore the functional relevance, we have developed an organotypic slice culture model of FCD using tissue resected from epileptic surgery and visualised them using 3D technique CLARITY. *Results:* Gene expression analysis identified 51 up-regulated secretory proteins in balloon cell dysplasias compared to normal cortex or non-balloon cell dysplasia. We performed immunohistochemistry for those that had the greatest differential expression and determined the identity of the expressing cells. Two of these markers were found in the distinct and unique cell populations, found mainly in the balloon cell dysplasias. In order to develop a functional model for cell-cell interactions, we developed organotypic cultures from patients undergoing neurosurgery for epilepsy. We also demonstrate the alteration of these molecules in the FCD IIb case after treatment with an mTOR inhibitor. *Conclusion:* We have identified novel cell-cell signalling pathways and developed a model to determine the functional roles of these interactions. This provides a generalisable approach to understanding cellular heterogeneity in developmental disorders of the brain.

Galactosialidosis: clinicopathological features of four autopsied patients

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Introduction: Galactosialidosis (GS) is a rare autosomal-recessive lysosomal storage disorder. The aim of the present study is to clarify the clinicopathological features of GS. **Methods:** We examined four autopsied patients with GS, one with the late infantile (LI) type (Case 1, aged 13 years) and three with the juvenile/adult (J/A) type (Cases 2-4, aged 51-71 years). All had homozygous mutations in CTSA (IVS3 (Case 1) and IVS7 (Cases 2-4)). **Results:** All of the patients had visual disturbance, myoclonus, cerebellar ataxia, and gargoylism. Other symptoms included psychomotor retardation (Case 1) and pyramidal signs (Cases 1, 3, and 4). In the late stage of illness, cognitive regression/dementia (Cases 1, 3, and 4), muscle weakness (Case 3), and autonomic dysfunction (Case 3) were noted. Pathologically, all four cases showed neuronal swelling throughout almost the entire CNS, as well as in the peripheral autonomic ganglia, whereas neuron loss was limited to more restricted areas. The LI-type patient showed severe neuronal loss in the motor cortex, thalamus, globus pallidus, and cerebellar molecular layer. In the J/A type, degenerative lesions were limited to the cerebellum and spinal ganglia in the youngest patient (Case 2), and then appeared to extend to the cerebral cortex, globus pallidus, Meynert nucleus, and spinal anterior horns in the older patients. Lewy bodies were commonly observed in the J/A subtype. **Conclusion:** Patients with GS show diverse clinicopathological features depending on the subtype or location of the mutations. In the J/A subtype, age may influence the distribution of the degenerative lesions.