O6-1

Ultrastructural mechanisms of macrophage-induced demyelination in chronic inflammatory demyelinating polyneuropathy: an observation on longitudinal sections

Haruki Koike, Yuki Fukami, Ryoji Nishi, Shohei Ikeda, Yuichi Kawagashira, Masahiro Iijima, Masahisa Katsuno, Gen Sobue

Nagoya University Graduate School of Medicine

Introduction: Although recent advances in the search for autoantibodies against components expressed at the nodes of Ranvier and the paranodes have significantly contributed to clarifying the pathogenesis in a subpopulation of chronic inflammatory demyelinating polyneuropathy (CIDP) patients, the mechanisms of neuropathy in cases with classical macrophage-induced demyelination remain unclear. Methods: We examined longitudinal sections of sural nerve biopsy specimens from 13 patients with CIDP who exhibited macrophage-associated myelin lesions using electron microscopy. In addition to the patients with typical CIDP, three patients with atypical CIDP were also included. To assess the relationship of macrophage-associated myelin lesions to nodal regions, a total of 1,159 nodes of Ranvier, with middle portions that were cut perpendicularly, were identified for examination. Results: As a whole, we found 116 macrophage-associated myelin lesions in longitudinal sections. Of these, 39 lesions were completely demyelinated, without being associated with the nodal regions or lamellar structures of the myelin. In 90 lesions, association with the nodes of Ranvier or paranodes was not observed. In the other 47 lesions, the involvement of nodal regions was obvious. The location of such macrophage-associated lesions appeared to deviate toward a particular segment of myelinated fiber depending on the individual case. The site that macrophages select to initiate myelin breakdown is located around the nodal regions in some patients and the internode in others. Conclusions: It seems that components that distinguish between the nodal regions and the internode play a pivotal role in the behavior of macrophages that initiate demyelination.

O6-2

Morphometric study of myelinated fibers in sural nerve of transthyretin familial amyloid neuropathy asymptomatic carriers: back to the archives of the Corino de Andrade Unit

Armindo Fernandes[1], Teresa Coelho[2], Helena Felgueiras[3], Aurora Rodrigues[4], Pedro Oliveira[1], Antonio Guimaraes[1,4], Manuel Melo Pires[1,4], Ricardo Taipa[1,4]

[1] Institute of Biomedical Sciences Abel Salazar, University of Porto, Portugal,
[2] Unidade Corino de Andrade, Department of Neurosciences, Centro Hospitalar do Porto,
[3] Department of Neurology, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal,
[4] Neuropathology Unit, Department of Neurosciences, Centro Hospitalar do Porto

Introduction: Familial amyloid neuropathy (FAP) with transthyretin V30M mutation (FAP-TTR) is the most common type of FAP. The mechanisms of nerve fiber loss in FAP have not been fully understood. An early description of pathological features in asymptomatic carriers has already disclosed abnormal findings in more than 50% of this population (Leite I, et al;1987). We recovered the archived biopsies of this study, performed additional morphometric studies and correlated this with the large clinical follow-up now available. Methods: Sural nerve biopsies from 83 FAP patients, 35 FAP asymptomatic carriers and 23 controls, age between 19 and 78 years, were compared. Results: Mean age at biopsy was 48.2 (14.9 SD) for patients, 33.5 (13.9 SD) for asymptomatic carriers and 48.6 (18.6 SD) for controls. The mean duration between nerve biopsy and symptoms onset was 9.2 (7.6 SD; range from 1 to 27 years). As expected, FAP patients had loss of all fiber type modalities compared to both asymptomatic carriers and controls ($p < 0.001$). Interestingly, the asymptomatic carriers showed loss of small myelinated fibers when compared to controls ($p < 0.01$). There was a positive correlation between myelinated fiber density and time to disease onset in the asymptomatic carriers that developed early-onset form of the disease ($p < 0.01$). Conclusions: This study confirms that small fiber size loss is an initial event in FAP-TTR, already present in asymptomatic gene carriers, starting several years before symptoms onset. These findings urge better ways to define disease onset to start treatment earlier.

O6-3

Fluoxetine improves regenerative capacity of the skeletal muscle

Mylene Fefeu[1,2], Pierre Rocheteau[1,2], David Briand[2], Gregory Jouvion[2], Olivier Mir[3], Katherine Nautiyal[4], Tarek Sharshar[2,7], Raphael Gaillard[1,5], Fabrice Chretien[2,5,6]

[1] Centre Hospitalier Sainte-Anne, Service Hospitalo Universitaire de psychiatrie, Paris, France,
[2] Institut Pasteur, Experimental Neuropathology Unit, Infection and Epidemiology Department, Paris, France,
[3] Department of Cancer Medicine, Gustave Roussy, University of Paris Sud, Villejuif, France,
[4] Division of Integrative Neuroscience, New York State Psychiatric Institute, and Department of Psychiatry, Columbia University, NY, USA.,
[5] Universite Paris Descartes, Sorbonne Paris Cite, Paris, France,
[6] Centre Hospitalier Sainte-Anne, Service Hospitalo Universitaire de neuropathologie, Paris, France,
[7] Service de reanimation medico-chirurgicale adulte, Hopital Raymond Poincare, Garches, France

Introduction: Antidepressants such as fluoxetine are widely used to treat mood disorders. The mechanisms of action include an increase of serotonin level, neurogenesis and angiogenesis in the brain. In line with these effects, we tested whether the antidepressant could have broader regenerative properties. Methods: To assess the effect of antidepressant on mice skeletal muscles, we administered fluoxetine at 18mg/kg daily for 6 weeks, followed by histological and cytometry analysis. To investigate whether fluoxetine may influence the regenerative capacity of skeletal muscles, we delivered fluoxetine for 6 weeks and performed a notexin-mediated muscle injury of in Tg:Pax7-nGFP mice in which the GFP reporter gene marks all muscle stem cells. To determine the mode of action of fluoxetine we performed the RT-qPCR for serotonin receptor subtypes on Tg:Pax7nGFP satellite cells isolated by FACS and then confirmed their involvement in fluoxetine effects on muscle regeneration by using specific antagonists of serotonin receptors. Finally, we tested whether fluoxetine had a potential therapeutic effect on Duchenne muscular dystrophy (DMD) by treating old mdx mice with fluoxetine for 6 weeks and performed histological and functional analysis. Results: Fluoxetine increased the number of muscle stem cells and improved skeletal muscle regeneration following injury. Beneficial effects of fluoxetine acted via the 5HT1b receptor directly on the muscle stem cells. Fluoxetine also decreased the number of lesions and increased the strength in a DMD model. Conclusion: These results suggest a potential clinical application for fluoxetine in dystrophic diseases and in organs displaying regenerative capacities, such as the skeletal muscle.

O7-1

The genetic landscape of pediatric low-grade gliomas: incidence, prognosis and response to therapy - a SickKids pLGG Task Force Update

Cynthia Hawkins[1,2], Scott Ryall[2], Michal Zapotocky[3], Kohei Fukuoka[3], Ana Guerreiro-Stucklin[3], Eric Bouffet[3], David Ellison[4], Uri Tabori[3]

[1] Department of Paediatric Laboratory Medicine, The Hospital for Sick Children,
[2] Laboratory Medicine and Pathobiology, The University of Toronto,
[3] Division of Haematology-Oncology, the Hospital for Sick Children,
[4] Pathology Department, St Jude Children's Research Hospital

Molecular characterization of pediatric low-grade glioma (pLGG) over the last decade has identified recurrent alterations, most commonly involving BRAF. Many of these molecular markers have been exploited clinically to aid in diagnosis and treatment decisions. However, their frequency and prognostic significance remain unknown. Further, a significant proportion of cases do not have any of these alterations and what underlies these cases is also unknown. To address these questions we compiled a cohort of 593 patients diagnosed with pLGG at SickKids from 2000-2017 of which 117 were non-biopsied NF-1 and 521 had sufficient tissue for molecular analysis. We identified molecular alterations in 419 cases (81% of the cohort). The most frequent events were those involving BRAF; either as fusions (most commonly with KIAA1549 (31%)) or V600E mutations (14%), and NF-1 (22%). Less frequently, we identified FGFR1 fusions and mutations (3%), MYB/MYBL alterations (2%), H3F3AK27M (2%) or IDH1R132H (0.5%) mutations, as well as other novel rare events. Survival analysis revealed significantly better progression-free survival (PFS) and overall survival (OS) of KIAA1549-BRAF fused patients compared to BRAFV600E with 10-year OS 97.7% (95%, CI 95.5-100) and 83.9% (95%, CI 72.5-95.6), respectively. In patients with MYB/MYBL1 or FGFR1/FGFR2 alterations, we observed only one death (FGFR1N546K case). While patients with H3F3AK27M had median PFS of only11 months. Beyond survival, molecular alterations predicted response to conventional therapeutics; BRAF fused patients showed a 46% response-rate, versus only 14% in V600E patients. This represents the largest cohort of molecularly profiled pLGGs and their impact on clinical behaviour.

O7-2

Improved diagnostic algorithm for differential diagnostics of CNS embryonal tumors (former CNS-PNET) by neuropathological re-evaluation of 256 cases and crossvalidation by methylation classification

Torsten Pietsch[1,2], Dominique Figarella-Branger[3], Felice Giangaspero[4], Cynthia Hawkins[5], Thomas S Jacques[6], Charles Eberhart[7], Peter Burger[7], Marcel Kool[8], Katja von Hoff[9], Christine Haberler[10]

[1] Institute of Neuropathology, University of Bonn, Germany, [2] DGNN Brain Tumor Reference Center,
[3] Department of Pathology and Neuropathology, Aix Marseille University, France,
[4] Department of Pathology, Sapienza University Rome, Italy, [5] The Hospital for Sick Children, Toronto, Canada,
[6] UCL Great Ormond Street Institute of Child Health, London, U.K.,
[7] Department of Pathology, Johns Hopkins University, Baltimore, USA, [8] DKFZ, Heidelberg, Germany,
[9] Department of Pediatric Hematology/Oncology, Hamburg University Medical Center, Hamburg, Germany,
[10] Department of Neuropathology, University of Vienna, Austria

Introduction: Epigenetic profiling has shown that a proportion of cases diagnosed as CNS-PNET in the past can be assigned to other tumour entities with similar morphological appearance. *Methods:* In an international effort to re-analyze CNS-PNET aiming for disease-specific re-evaluation of survival data and the development of diagnostic guidelines providing the basis for improved therapeutic approaches, 256 tumours diagnosed and treated as CNS-PNET in the last two decades in 17 countries were reviewed by a panel of neuropathologists according to today's standards of clinical neuropathological diagnostics including immunohistochemical and molecular pathological assays. The majority of cases were also independently analyzed by methylation array hybridization and classified by random forest algorithm. *Results:* In this unique cohort, we identified 20 different tumor entities including frequent high grade gliomas. 41% of cases were confirmed as CNS-PNET (now termed CNS-embryonal tumors (CNS-ET) according to the revised WHO-classification) representing two main entities: ETMR displayed typical histological features, LIN28A expression and/or *C19MC* alteration. The other represented a group of tumors with variable degrees of neuroblastic/ganglionic differentiation, corresponding to the WHO diagnoses CNS-(Ganglio)-neuroblastoma or CNS-ET, NOS. The vast majority of these tumors could be assigned to the FOXR2 CNS-NB group by methylation array-based classification. *Conclusions:* Crossvalidation of neuropathological and epigenetic classification proved that methylation classification represents a useful complimentary tool in the differential diagnosis of CNS-ET. Re-evaluation of prototypic tumors and discrepant cases enabled us to develop an optimized diagnostic algorithm to securely delineate this tumor from other entities with largely divergent clinical and biological behaviour.

O7-3

Value of Immunohistochemistry and Sequencing for Detection of the H3.3 G34 Mutations in High Grade Gliomas

Francesca Gianno[1,6], Manila Antonelli[1], Tiziano Di Dio[1], Francesca Diomedi[2], Anna Maria Buccoliero[3], Mariangela Novello[4], Vittoria Donofrio[5], Francesco Fiorentino[1], Antonella Arcella[6], Felice Giangaspero[1,6]

[1] Department of Radiological, Oncological and Anatomo-pathological Sciences, University Sapienza, Rome, Italy,
[2] Department of Laboratories, Pathology Unit, Bambino Gesu Children's Hospital, IRCCS,
[3] A. Meyer Children's University Hospital, Pathology Unit , Florence, Italy,
[4] Anatomic Pathology Unit, Vicenza Hospital, Vicenza, Italy,
[5] Anatomic Pathology Unit, Santobono-Pausilipon Children's Hospital, Naples, Italy,
[6] IRCCS Neuromed, Pozzilli, Italy

Introduction: Recurrent glycine-to-arginine/valine alterations at codon 34 (G34R/V) within H3F3A gene occur in hemispheric high grade gliomas (HGG) of children/young adults. These tumors are histologically heterogeneous, with microscopic features of either glioblastoma/anaplastic astrocytoma (GBM/AA) or embryonal tumors (PNET-like). To assess the value of immunohistochemistry (IHC) to detected H3.3G34 mutated cases, we tested an anti-histone H3.3G34V (Clone329E5) and anti-histone H3.3G34R (CloneRM240) antibodies in a series of 25 formalin fixed and paraffin-embedded (FFPE) samples.Methods. Twenty-five cases of HGG were evaluated by immunohistochemistry and 17/25 by sequencing. The median age was 19 years (4-78 years). All cases were hemispheric. Histologically 20/25 were GBM/AA and 5/25 cases were PNET-like. Results. By immunohistochemistry, 8/25 cases showed nuclear positivity for H3.3G34R and 1/25 for H3.3G34V. By targeted sequencing, performed in 17/25 cases, 7/17 cases showed mutations: 6 H3.3G34R and 1 H3.3G34V. All 7 cases mutated by sequencing resulted positive by IHC. However, two out nine cases positive by IHC resulted wild type by sequencing. Moreover, 6/7 of mutated cases showed loss of ATRX expression and/or p53 expression, and 1/7 was ATRX-positive and p53-negative. All cases were negative for IDH mutations.Conclusion: 1) Positivity by IHC is highly predictive for H3.3 G34 mutation but confirmation by sequencing is mandatory; 2) Negativity by IHC indicates absence of mutations; 3) H3.3 G34 mutations should be suspected in all hemispheric tumor IDH1/2 wild type, showing loss of ATRX and/or p53 expression.

O7-4

Grading of pediatric high grade gliomas. Results from the HERBY trial

Pascale Varlet[1], Gwenael Le Teuff[2], Marie-Cecile Le Deley[3], Felice Giangaspero[4], Christine Haberler[5], Thomas Jacques[6], Dominique Figarella-Branger[7], Torsten Pietsch[8], Felipe Andreiuolo[1], Jacques Grill[2]

[1] Department of Neuropathology, Sainte-Anne Hospital, Paris, France, [2] Institut Gustave Roussy, Villejuif, France, [3] Centre Oscar Lambret, Lille, France, [4] Sapienza University of Rome, Roma andIRCCS Neuromed, Pozzilli (Is), [5] Institute of Neurology, Wien, Austria,
[6] UCL GOS Institute of Child Health and Great Ormond Street Hospital, London, United Kingdom,
[7] Hopital de la Timone, Marseille, France, [8] University Bonn, Bonn, Germany

The glioma grading system initially designed for diffuse adult gliomas is questionable in pediatric high grade gliomas (HGG), which are biologically distinct from their adult counterparts. This issue was addressed from HERBY randomized phase-II trial (NCT01390948) with newly-diagnosed non-brainstem HGG Methods: A real-time central pathology review (WHO-2007) was mandatory before randomization, followed by a consensus review including five other independent experts. We evaluated the inter-observer agreement for grading (Kappa coefficients); the discriminant ability of elementary grading criteria associated with III / IV grade (logistic regression); the prognostic value of grade, midline location and selected biomarkers (Mib-index, CD34, EGFR, p53, H3K27Mut) on event-free survival (EFS) and overall survival (OS) (Cox models). Findings: Among the 124 evaluable cases, inter-observer agreement was substantial for HGG-grading (Kappa=0.81), vascular proliferation (Kappa=0.74) and necrosis (Kappa=0.85), but moderate for the four other criteria (differentiation, cellular density, atypia, mitosis: Kappa<0.60). Adding these four criteria did not significantly increase the discriminant ability as compared to the combination of vascular proliferation and necrosis (AUC=0.99 vs 0.97, p=0.24). High Mib-index was more frequent in grade-IV than in III. Among the 118 confirmed and randomized HGG, neither the different grading criteria, nor the resulting grade were found significantly associated with survival outcomes (in midline and non midline HGG). Midline location and a high Mib-index were both associated with poor EFS (HR=2.33 [95%CI=1.38-3.92] and 2.57 [1.39-4.74) and OS (HR=2.57 [1.36-4.88] and 2.06 [1.04-4.10]) in multivariable analysis. Conclusion: These data highlight that WHO-grading for HGG is questionable in children with respect to prognostication

O7-5

Immunohistochemical and molecular subtyping of Central Nervous System Primitive neuroectodermal tumors (CNS PNETs) in light of the updated 2016 WHO classification

Mehar Chand Sharma[1], Niteeka Gurung[1], Amandeep Kumar[2], Vaishali Suri[1], Manmohan Singh[2], Chitra Sarkar[1]

[1] Department of Pathology, All India Institute of Medical Sciences (AIIMS), New Delhi,
[2] Department of Neurosurgery, AIIMS, New Delhi

Introduction: Poorly differentiated embryonal tumors previously designated as Central Nervous System Primitive neuroectodermal tumors (CNS PNETs) encompass heterogeneous entities with specific molecular alterations. Embryonal tumor with multilayered rosettes is one such subtype, characterized by C19MC amplification and lin28A immunoexpression (ETMR, C19MC altered). Those lacking specific molecular alterations are now termed CNS embryonal tumor, NOS. We aimed to reclassify CNS PNETs according to current WHO 2016 classification, and evaluate true incidence of CNS embryonal tumors, NOS, in a tertiary healthcare setting. Methods: CNS PNETs (negative for t(11:22), immunonegative for MIC2, RelaA, L1CAM, IDH1R132H, and H3K27M proteins, retained INI1) underwent immunohistochemistry for Lin28A and Olig2, and FISH for C19MC amplification. Ten cases each of medulloblastoma, ATRT, pineoblastoma, Ewing sarcoma and esthesioneuroblastoma were included as controls. Results: Among 22 cases of CNS PNETs included, 2 showed C19MC alteration (ETMR, C19MC altered). Both showed medulloepithelioma morphology and Lin28A immunopositivity. No other tumor, including controls, showed C19MC alteration, while 27% ATRTs showed false positive staining for Lin28A. 14% of CNS PNETs showed Olig2 positivity of which all showed classical morphology and were negative for C19MC amplification and Lin28A. None of the controls was Olig2 positive. Conclusion: Among CNS embryonal tumors, ETMR C19MC altered constitute less than 10% with majority remaining uncharacterized as CNS embryonal tumors, NOS. Lin28A is a sensitive immunohistochemical marker for identification of ETMR. However, its specificity is limited by its expression in ATRTs.

O8-1

High-grade gliomas involving the subventricular zone - a molecular study of 32 cases

Aden Ka-yin Chan, Riki Rui-qi Zhang, Ho Keung Ng

Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong

Introduction: High-grade gliomas abutting on the subventricular region have been described to show aggressive features and poor outcomes but there has been no detailed study of molecular features of these tumors.Methods: We studied 32 such tumors from our archives, all except one being glioblastomas, for their clinical features and examined amplifications of c-myc, MYCN, EGFR, mutations of H3F3A-K27M, TERTp, IDH1-R132H, 10q deletion and by immunohistochemistry ATRX, nestin and SOX2.Results: c-Myc and MYCN were each amplified in 32.3% and together were amplified in 58% of the cases. This is in contrast to information derived from TCGA dataset where c-Myc and MYCN were only rarely amplified in glioblastoma. MYCN in addition was associated with younger age (p=0.029), concomitant H3F3A-K27M mutation (p=0.002), non-amplified EGFR (p=0.023) and mid-line location (p=0.012). Interestingly, we found a low percentage of TERTp mutation (19%) among these high-grade gliomas which was mutually exclusive with a higher frequency of ATRX loss (p=0.025). The majority (91%) of tumors were IDH wildtype and 39% of them were deleted for 10q. Moreover, 97% of cases expressed at least one of the stem cell markers, which may be related to the supposedly subventricular location of neural stem cells. 89% of cases relapsed with 50% showing CSF dissemination. However, there was no statistical relationship between survivals and biomarkers or other clinical parameters.Conclusion: In conclusion, our study has identified a subgroup of subventricular zone high-grade gliomas characterized by c-Myc, MYCN amplification and frequent expression of stem cell markers and a high rate of CSF dissemination.

O8-2

INI-1 immunohistochemistry in CNS embryonal tumors - a clinicopathological study

Lily Pal[1], Ananth Mehrotra[2], Shalini Singh[3]

[1] Department of Pathology, SGPGIMS, [2] Department of Neurosurgery, SGPGIMS, [3] Department of Radiotherapy

Introduction : Central nervous system embryonal neuroepithelial tumors are highly malignant, heterogenous group of neoplasms and medulloblastoma is the most common entity in children. Nuclear expression of hSNF5/INI-1, a tumor suppressor gene is retained in medulloblastomas, pineoblastomas and other embryonal tumors enabling distinction from atypical teratoid/ rhabdoid tumor (AT/RT) with dismal prognosis. Embryonal tumors without rhabdoid morphology are often difficult to diagnose and hence this study was undertaken. Material & methods : 141 cases of CNS embryonal tumors were retrieved from the archives of Pathology SGPGIMS, comprising of medulloblastoma (103), pineoblastoma (4), AT/RT(15), Embryonal tumor with multilayered rosettes (ETMR 2), CNS neuroblastoma (1) and CNS embryonal tumor NOS(16). Immunohistochemistry for INI-1 protein was performed in all these cases along with GFAP, synaptophysin, desmin, Vimentin, EMA, SMA and cytokeratin as and when required. Results : Majority of medulloblastomas (94/103) expressed INI-1 and there was no significant difference across histological subtypes. One half of AT/RTs were in the age group of 9 months to 3 years and all showed loss of INI-1 protein. Immunohistochemically all AT/RTs had polyphenotypic nature and were negative for desmin. INI-1 was retained in rest of the embryonal tumors. Conclusion : Medulloblastomas and other embryonal tumors including AT/RTs often have clinical, radiological and histological overlapping features. Prognosis for patients with AT/RT is worse than other embryonal tumors due to poor response to conventional therapy. Therefore INI-1 immunohistochemistry routinely in all malignant pediatric embryonal may help to identify INI-1 negative tumors and may be benefit from accelerated treatment.

O8-3

Histopathologic description and identification of prognostic factors for infantile desmoplastic gangliogliomas and astrocytomas

Perbet Romain[1,2], Maurage Claude-Alain[1,2], Varlet Pascale[3], Jouvet Anne[5], Silva Karen[5], Gourmel Antoine[4]

[1] School of Medecine, University of Lille, France, [2] Pathology Institute, Lille University hospital, France,
[3] Department of Pathology, Sainte-Anne Hospital, France,
[4] Department of Pediatric Oncology, Amiens University Medical Center, Amiens, France,
[5] Service de Neuropathologie, Groupe Hospitalier Est, Hospices Civils de Lyon, , Lyon,, France

Introduction. Desmoplastic infantile gangliogliomas (DIG) and desmoplastic infantile astrocytomas (DIA) are rare cerebral tumors; their prognostic factors are not well established, especially regarding histopathological and molecular criteria. Methods. All DIG/DIA diagnosed in France from January 1998 to December 2016 were included in this retrospective study. The main objective was to assess the prognostic impact of histopathological and molecular criteria on progression-free survival (PFS). The following criteria were analyzed: necrosis (present vs. absent), microvascular proliferation (present vs. absent), mitotic count, cellular area (surface rate), poorly differentiated neuroepithelial component (surface rate), desmoplasia (surface rate), Ki-67 and olig2 labeling index, neuronal markers expression (present vs. absent), chromosomal alteration (CGH array) and BRAF mutation status . Results. 37 patients were included in this study. The 5-year overall survival and PFS were 93% and 72% respectively (median follow up of 57 months). Four patients died of disease and 13 patients relapsed. Total surgical resection was not associated with a higher PFS ($p = 0.88$). High mitotic count (HR = 1.189; $p < 0.001$), high Ki-67 labeling index (HR = 1.056; $p = 0.005$), high cellular area (HR = 1.017; $p = 0.019$), poorly differentiated neuroepithelial component (HR = 1.042; $p = 0.039$), any chromosomal alteration (HR = 4.890; $p = 0.021$) and BRAF mutation (HR = 4.350; $p = 0.020$) were associated with a lower PFS. Conclusions. These tumors display several microscopic features that can mimic high grade brain tumors. Standard stain examination, Ki-67 index, CGHarray and BRAF mutation status are of interest as predictors of outcome.

O8-4

Presence of H3 K27M mutation in a series of midline children/young adults gliomas

Jose Pimentel[1,2], Lucia Roque[3], Claudia Faria[4], Rafael Roque[1]

[1] Laboratorio de Neuropatologia, Servico de Neurologia, Departamento de Neurociencias, Hospital de Santa Maria,
[2] Faculdade de Medicina, Universidade de Lisboa,
[3] Unidade de Investigacao em Patobiologia Molecular, Instituto Portugues de Oncologia de Lisboa Francisco Gentil,
[4] Servico de Neurocirurgia, Departamento de Neurociencias, Hospital de Santa Maria,
[5] Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa

Introduction: Conventionally, gliomas with the Histone H3-K27M mutation arise in children/young adults in the midline, and are linked to a poor prognostic unrespect the anaplasia degree. Material and methods: All gliomas arising in the midline in children/young adults with the presence of the mutation demanded during the diagnostic work-up. The following antibodies (abs) were performed: GFAP, Olig2, ATRX, IDH1, S100, MAP2, and P53. K27M mutation analysis was obtained by sequencing after the histological diagnosis. Results: Seven patients, 4 males, aged between 2 and 32 years, with gliomas in the spinal cord (1), pons (4), thalamus (1) and 3th ventricle (1). Histomorphological diagnostics were pylocitic astrocytoma (2), anaplastic astrocytoma (1), and glioblastoma (4). Surgeries were ressective (2) and stereotaxic biopsy (5). All patients did the standard postsurgery treatment. All patients died between 1 and 11 months after surgery. All cases were GFAP positive, IDH1 negative, and ATRX non mutated. For the rest of the abs, positivity for S100, Olig2 and MAP2 for all cases, and for P53 in 3. Discussion/Conclusion: The approach of this series was mainly the standard one and data was similar to previously ones regarding clinical, histopathology and immunohistochemistry features. Enlarged field of clinical and histomorphological gliomas`recruitment will probably increase the presence of H3-K27M mutation and change the paradigm of these tumors.

O8-5

An integrative radiological, histopathological and molecular analysis of pediatric pontine MYCN-HGG

Arnault Tauziede-Espariat[1], Marie-Anne Debily[2], David Castel[2], Stephanie Puget[3], Magnus Sabel[4], Klas Blomgren[5], Jacques Grill[2,6], Volodia Dangouloff-Ros[7], Nathalie Boddaert[7], Pascale Varlet[1]

[1] Department of Neuropathology, Sainte-Anne Hospital, Paris, France,
[2] UMR 8203 Vectorologie et Therapeutiques Anticancereuses CNRS, Gustave Roussy, Univ. Paris-Sud, Universite Paris-Saclay, Villejuif, France,
[3] Department of Paediatric Neurosurgery, Necker Hospital, APHP, Universite Paris Descartes, Sorbonne Paris Cite, Paris, France,
[4] Department of Paediatric Oncology, Childhood Cancer Centre Queen Silvia Children's Hospital Sahlgrenska University hospital, Goteborg, Sweden,
[5] Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden,
[6] Departement de Cancerologie de l Enfant et de l Adolescent, Gustave Roussy, Univ. Paris-Sud, Universite Paris-Saclay, Villejuif, France,
[7] Department of Radiology, Necker Hospital, APHP, Universite Paris Descartes, Sorbonne Paris Cite, Paris, France

Introduction: Diffuse midline glioma, H3K27M-mutant was recently introduced in the 2016 WHO classification of CNS tumors and represents the main tumoral glial subgroup located in the brainstem. However, 2 rare groups of brainstem gliomas without histone gene mutations have also been described: the MYCN-HGG and the silent-subgroups. The aim of this study was to perform a detailed clinicoradiologic and histomolecular study of MYCN-HGG of the brainstem. Methods: A central radiological and pathological review with routine biomarkers assessment was performed. FISH analysis of MYCN and whole exome sequencing on cryopreserved tissue were also performed. Results: All 6 tumors presented as a nodular mass with annular enhancement on MRI. These tumors were morphologically poorly differentiated with spindle cells. They did not express H3K27M, Lin28A, or BCOR. No loss of H3K27me3, INI1 and BRG1 were observed. The immunohistochemical pattern showed no or focal expression of glial markers (GFAP and Olig2) and a constant expression of at least one neuronal marker. Four tumors overexpressed p53. All tumors presented with an amplification of MYCN and ID2 genes. FISH analysis confirmed the presence of a MYCN amplification in 4/6 cases. Conclusion: we described detailed clinicoradiologic and immuno-morphologic features of 6 cases of pontine MYCN-HGG, thereby highlighting the consistent amplification of MYCN and ID2 genes. This diagnosis must be considered when microscopic features reveal a highly malignant undifferentiated tumor without loss of H3K27me3 trimethylation. Distinguishing this rare neoplasm from diffuse midline glioma, H3K27M-mutant might allow for establishing targeted molecular therapies in the future.

O9-1

The UCLA brain tumor bank: a comprehensive approach including autopsies, sGluc-GFP xenografts and ethnic diversity

William H Yong[1], Robert M Prins[2], Richard G Everson[2], Won Kim[2], Harry V Vinters[1,3], Albert M Lai[3], Phioanh L Nghiemphu[3], Timothy F Cloughesy[3], Linda M Liau[2], David A Nathanson[4]

[1] Dept of Pathology (Neuropathology), UCLA School of Medicine,
[2] Dept of Neurosurgery, UCLA School of Medicine,
[3] Dept of Neurology (Neuro-oncology), UCLA School of Medicine,
[4] Dept of Molecular and Medical Pharmacology, UCLA School of Medicine

Introduction: The incidence of glioblastoma in U.S. non-Latino Whites is higher than in Latinos who in turn have a higher incidence than Asians or African-Americans. Latinos have lower rates of gross total resection and radiation, yet have better survival. IDH1 and MGMT status are not different from non-Latino Whites. As Latinos are a large minority population, understanding their GBM biology and therapy is particularly important.
Methods: Consents are available in English and Spanish. Neuropathologists and on call-technicians procure blood, surgical tissue and autopsy brains from glioma patients, mostly GBM patients. For surgical specimens, we routinely introduce a lentiviral reporter, secreted Gaussia luciferase tagged to GFP (sGLUC-GFP), into live tumor cells and then generate glioma patient derived orthotopic xenografts (glioma PDOX).
Results: Tumor burden is accurately measured by serial blood sGLUC-GFP measurements without need of MRI imaging. These glioma PDOXs preserve the diversity of genetic, transcriptional and immunohistochemical signatures, and are useful for testing therapies. There are over 100 autopsies and over 70 xenografts representing mostly Whites but also Latinos and other minorities. Glioma autopsies can provide data on the evolutionary endpoint of the patient's GBM.
Conclusion: As most procured tumors are from non-Latino White patients, efforts are being made to recruit more minority patients. Other countries may have unique minorities that do not have GBM biology identical to the majority and that are worth considering for recruitment and study.

O9-2

mTORC2-dependent metabolic reprogramming facilitates epigenetic regulation of iron trafficking in glioblastoma

Kenta Masui[1], Paul S Mischel[2], Noriyuki Shibata[1]

[1] Department of Pathology, Tokyo Women's Medical University, [2] Ludwig Institute for Cancer Research, UCSD

Introduction: Hyper-activated growth factor receptor signaling, frequently observed in cancer, reprograms cellular metabolism and global gene transcription, but the underlying mechanisms are not well clarified. Here, we endeavored to examine the role of glycolytic metabolism in the regulation of epigenetics in glioblastoma (GBM). Methods: To unravel the functional consequences of cancer metabolic reprogramming on epigenetics, we interrogated cell lines, mouse tumor models, and clinical samples of GBM, the highly lethal malignant brain tumor in human. Results: mTORC2 (mechanistic target of rapamycin complex 2) signaling facilitated acetyl-CoA production as well as nuclear translocation of histone modifying enzymes including PDH (pyruvate dehydrogenase) and class IIa HDACs (histone deacetylases), resulting in histone H3 acetylation of the ferritin promoter, maintenance of iron trafficking and cancer cell survival. In clinical human samples, mTORC2 signaling was highly correlated with histone acetylation and elevated ferritin expression, indicating mTORC2-dependent epigenetic regulation of iron metabolism in GBM patients. Conclusion: In GBM, mTORC2 integrates aberrant growth factor receptor signaling and cellular metabolism with reprogramming of epigenetic landscapes, which drives tumor growth through H3 acetylation in the promoter of iron trafficking genes to promote iron metabolism for tumor cell survival.

O9-3

Identification of novel gene fusions in glioblastomas with chromothripsis

Audrey Rousseau[1,2], Blandine Boisselier[1,2], Philippe Guardiola[2,3], Emmanuel Garcion[2], Philippe Menei[2,4], Franck Ah-Pine[1]

[1] Departement de Pathologie Cellulaire et Tissulaire, CHU Angers, Angers, France,
[2] CRCINA, INSERM, Universite de Nantes, Universite Angers, Angers, France,
[3] SERGOH, CHU Angers, Angers, France, [4] Departement de Neurochirurgie, CHU Angers, Angers, France

Introduction: Glioblastoma (GBM), the most aggressive form of glioma, harbors chromosome instability. Chromothripsis (CT) is a cataclysmic event whereby massive chromosome shattering occurs during a single mitotic event. A single or a few chromosomes are shattered and then randomly reassembled in a derivative chromosome. This one-step event may lead to the inactivation of tumor suppressor genes, the activation of oncogenes and/or the generation of oncogenic fusion genes. CT might underlie the development of GBM and accelerate disease progression. The aim of our study was to identify novel fusion genes in a cohort of GBM harboring CT.
Methods: 280 GBM were previously analyzed by SNP array to detect CT. RNA sequencing (RNAseq) was performed in cases with CT patterns, leading to the identification of candidate fusion genes in CT regions. Gene fusions were confirmed by RT-PCR followed by Sanger sequencing.
Results: SNP array analysis showed CT patterns in 90 GBM (32%). RNAseq was performed in 32 cases displaying 50 candidate fusion genes in CT regions. RT-PCR followed by Sanger sequencing confirmed the presence of novel in-frame fusions, involving key oncogenes such as *EGFR*, *MDM2* and *MET* but also genes (*VOPP1*, *HMGA2*, *SEC61G*) with yet-to-discover role in GBM pathogenesis.
Conclusion: The occurrence of CT points to underlying gene fusions in GBM. Such fusions may drive tumor cell proliferation and survival and may represent therapeutic targets. Our results provide new perspectives to better understand GBM pathogenesis and treat this fatal disease.

O9-4

Haemangioblastoma and other vascular changes; clinical pathological and immunohistochemical approaches. Clinical, pathological and immunohistochemical approaches

Martha Lilia Tena-Suck[1], Leora Velasquez-Perez[2], Carlos Sanchez-Garibay[1]

[1] Department of Neuropathology, National Institute of Neurology and Neurosurgery,
[2] Epidemiology Service. National Institute of Neurology and Neurosurgery

Introduction. Haemangioblastoma is a tumor of the CNS that originate from blood vessels and usually through middle-age. Methods. This work was a clinic pathological and immunohistochemistry approaches of haemangioblastoma with special emphasis with other vascular changes like, arteriovenous malformations, fibromuscular dysplasia and bigger vessels what we call them as call them as vascular anomalies. Results. 46 cases were included in this study. 24(52%) females and 22(48%) male, patient history of VHLD in 13(28.3%) and familial history of VHLD in 22 (48%). Histological type was; cellular pattern 20 (46%) and reticular pattern 26(57%), gross vessel was observed a weak or scares in 28(61%) and moderate in 18(39%), in addition. Those gross vessels were observed with Masson and reticulin stain. Vessels anomalies were observed in VHLD than sporadic tumors and in recurrence. Nuclear pleomorphism, nuclear cytoplasmic inclusions, cytoplasmic vacuolation are noted in the stromal cells, and higher Ki67-li that were in tumor whit vessels anomalies than tumors with VA, and were positive for inhibin A, CD56, vimentin, INI-1, and VEGF, HIF α, CD56, NSE, Syn, CgA, EMA, exrin, aquaporin, and brachyury. There was not statistical significance with different antibodies used. Conclusion. Recent data indicate that VHL-associated hemangioblastoma neoplastic cells originate from embryologically-arrested hemangioblasts capable of blood and endothelial cell differentiation as well as alterations of the vascular wall. We could say that it is a stromal stem cell tumor in a varied stage of differentiation.