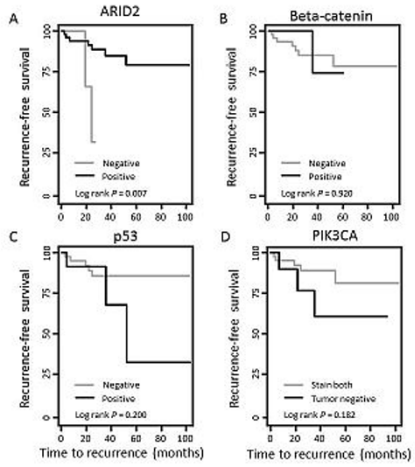
PIK3CA in HCC is a novel finding and further investigations may determine if this represents feedback inactivation of the mTOR pathway.



1720 Aberrant von Willebrand Factor (vWF) Expression of Sinusoidal Endothelial Cells in Nodular Regenerative Hyperplasia and Obliterative Portal Venopathy

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Background: Nodular regenerative hyperplasia (NRH) and obliterative portal venopathy (OPV) are under-recognized diseases of uncertain etiology that result in noncirrhotic portal hypertension (NCPH). The diagnosis can be easily missed on needle liver biopsy. CD34 and vWF are commonly used endothelial markers. vWF is released by activated endothelial cells and plays a crucial role in primary hemostasis and in the development of thrombotic vascular obliteration. Liver sinusoidal endothelial cells (LSEC) are unique in that the expression of CD34 and vWF are confined only to periportal areas in the normal liver. We sought to investigate the potential utility of these two immunomarkers in helping make the diagnosis of NRH and OPV. Additionally, the immunoexpression pattern may further elucidate the pathogenesis of these conditions.

Design: Re-review of the histology of liver wedge and needle biopsies of clinically proven NCPH cases was undertaken. NRH is defined as small hyperplastic nodules centered around portal tracts compressing adjacent atrophic hepatocytes and sinusoids whereas OPV, although having heterogeneous histology, commonly demonstrates different degrees of phlebosclerosis and dense portal fibrosis. Cases with combined OPV and NRH on biopsy were also noted. Immunohistochemical staining for CD34 and vWF (DAKO, Carpinteria, CA) was performed using standard methods.

Results: There were 15 NRH, 25 OPV and 5 normal liver biopsies (acting as controls). Among the 25 OPV, 20 had concurrent features of NRH (80%). CD34 (+) staining was mainly confined to small vessels in the portal tracts as well as LSECs in periportal areas in both NRH and OPV, similar to that in the normal control biopsies. Unlike CD34, expression of vWF in LSECs was (+) along the dilated sinusoids of NRH, and in a patchy or geographic pattern, particularly prominent in the perivenular areas of OPV as opposed to vWF expression being confined to periportal areas in the controls.

Conclusions: NRH and OPV are commonly seen together in the same liver biopsy. The aberrant expression of vWF in NRH and OPV suggest that LSEC activation is involved in their pathogenesis and that NRH and OPV may share a common pathway of vascular injury. The aberrant expression pattern of vWF may also aid in the histologic diagnosis and recognition of NRH and OPV on liver biopsy.

1721 The p53 Negative Regulator, MDM4 but Not MDM2, Is Frequently Activated in Hepatocellular Carcinoma

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Background: The p53 tumor suppressor pathway is frequently inactivated in human cancers including hepatocellular carcinoma (HCC). MDM2 and MDM4 are the primary negative regulators of p53. Amplification or over-expression of MDM2 and MDM4 abolish the p53 mediated response by inactivating the wild-type p53 protein. A functional single nucleotide polymorphism of the *MDM2* (SNP-309 T/G) enhances the Sp1 binding to *MDM2* promoter and MDM2 expression resulting in attenuation of p53 and has been associated with the development and prognosis of a number of tumors. We hypothesized that over-expression of MDM2 and MDM4 may be the common mechanism of p53 inactivation in HCC and thus a potential therapeutic target.

Design: Tissue microarrays of HCC were constructed and immunohistochemically stained for MDM2, MDM4 and p53. Expression intensity was scored as 0 (absent), 1+ (modest) or 2+ (high). Genotyping of *MDM2* SNP-309 was performed on genomic DNA extracted from tumor by PCR amplification flanking the corresponding promoter region followed by temperature gradient capillary electrophoresis and direct sequencing. We evaluated the association between *MDM2* SNP-309 and the risk of HCC by comparing the genotype frequency with that of controls. We also investigated the relationships between *MDM2* SNP-309 genotype, MDM2, MDM4 and p53 expression and median overall survival time.

Results: MDM4 expression was detected in 42 of 93 HCC (45%; 1+ in 33, 2+ in 9), p53 was detected in 6 (6%; 1+ in 4, 2+ in 2), and no MDM2 immunoreactivity was found. The *MDM2* SNP-309 genotypes of HCC were not statistically different from those of 100 controls.

MDM2 SNP-309 Genotypes in HCC and Controls

	HCC (n = 69)	Control (n = 100)
G/G	7 (10%)	12 (12%)
T/G	30 (43.5%)	40 (40%)
T/T	32 (46.4%)	48 (48%)

p = 0.981

No correlation was observed between *MDM2* SNP-309 genotype, MDM4 and p53 expression level and median overall survival time.

Conclusions: Aberrant activation of MDM4 is frequently present in HCC and could represent a common mechanism by which wild-type p53 is inactivated. It is unlikely that *MDM2* SNP-309 or over-expression of MDM2 contribute to p53 inactivation. We are currently evaluating the potential mechanism of MDM4 over-expression and the correlation with p53 mutation status.

Neuropathology

1722 Altered Telomeres with Loss of *ATRX* Protein Are Frequently Seen in High-Grade Pediatric Gliomas

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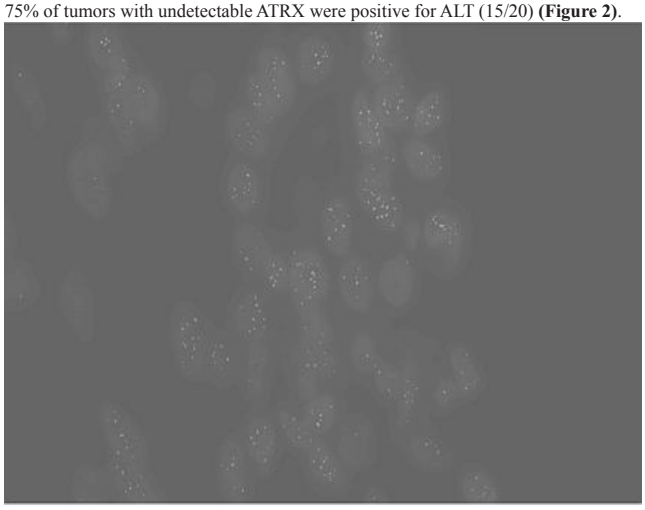
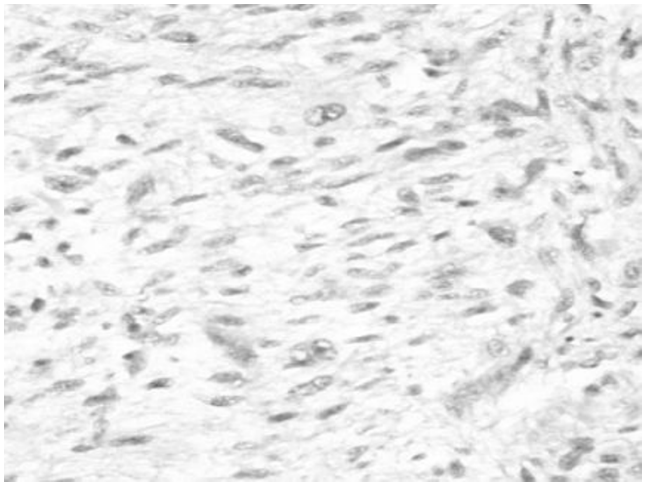
Background: Loss of function of alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein leads to a phenotype called alternative lengthening of telomeres (ALT). Mutations that inactivate these genes are common in human pancreatic neuroendocrine tumors (PanNETs) and CNS tumors.

Design: We examined 60 cases of high-grade pediatric gliomas of various histological types and looked for loss of ATRX with immunocytochemistry and the presence of ALT with telomere-specific fluorescence in situ hybridization.

Results: Using a large cohort from multiple institution of high-grade pediatric gliomas (n = 60) we found that 33.33% of tumors were ALT positive (20/60) **(Figure 1)**, and 75% of tumors with undetectable ATRX were positive for ALT (15/20) **(Figure 2)**.





Conclusions: Further understanding of the role of ATRX/DAXX and histone H3.3 in GBM pathogenesis may lead to more accurate prognosis and stratification of patients to the most appropriate therapies. ALT/ATRX may serve as a potential screening and prognostic marker in patients with pediatric gliomas. Our results show that telomere-

specific FISH and ATRX staining are reliable assays of choice for formalin-fixed tissue. Other genetic markers in addition to *ATRX* may help classify patients, leading to more accurate prognosis and more successful treatment strategies. In addition, targeting molecules that play a role in chromosome remodeling and telomere stability, including telomerase and ALT-related proteins, may be a strategy for developing new treatments for these highly aggressive pediatric cancers. Finally, our data highlight the distinction between adult and pediatric gliomas.

1723 Canonical TGF-Beta Pathway Activity Is a Predictor of SHH-Driven Medulloblastoma Survival

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Background: Medulloblastoma, an embryonal neuroepithelial tumour arising in the cerebellum, is the most common malignant brain tumor of childhood. Although current treatment regimens have significantly improved survival over the past decades, recurrent and/or metastatic MB still spell poor prognosis for patients. Aggressiveness is marked by increased growth and decreased responsiveness to available therapies. However the molecular changes that underlie these pathophysiological behaviors during medulloblastoma progression are not well understood.

Design: To further identify pathways of signaling that contribute to medulloblastoma metastasis and recurrence we decided to undertake an unbiased, whole genome expression study. We performed microarray experiments, using human patient matched primary and recurrent or metastatic samples. This was supplemented with microarray data derived from murine samples from two different mouse models of medulloblastoma, the Ptch+/- and Smo/Smo models, that present with differing clinical histories and disease aggressiveness.

Results: At both the human and murine levels we identified the Transforming Growth Factor-beta (TGF-beta) as a potential contributor to medulloblastoma progression/metastasis. Smad3, a major downstream component of the TGF-β pathway, was also evaluated using immunohistochemistry in both developing and malignant human and murine tissue and was shown to correlate with disease progression. Currently we are in the process of assessing the contribution of this signaling pathway in an *in vitro* setting.

Conclusions: This work identifies TGF-β as a potential contributor to medulloblastoma progression and metastasis both at the level of RNA and protein expression in the human and murine species. To our knowledge, this is the first study that implicates TGF-β as a contributor to medulloblastoma progression and metastasis.

1724 Frontotemporal Lobar Degeneration (FTLD): Updated Pathology and Co-Existing Neurodegenerative Phenomena in a Cohort of 52 Patients

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Background: The pathological classification of FTLD has drastically changed in the past few years with identification of intracellular proteins implicated in the disease. Multiple neurodegenerative phenomena often co-exist at autopsy yet their role in the etiology of FTLD and their impact on clinical phenotype is poorly understood. Our goals were to examine CNS autopsy cases collected over the last 13 years with FTLD, update the pathological classification and document co-existing neurodegenerative phenomena.

Design: The archives at SHSC were searched for autopsy cases since 2000 with a diagnosis of FTLD who were assessed at the SHSC Cognitive Neurology Clinic (N = 52). The FTLD type and subtype were revised according to the recent FTLD classification scheme using the original autopsy slides and immunohistochemistry (IHC) for TDP43, p62, & tau (AT8). Cases were screened for co-existing Alzheimer's pathology (beta-amyloid and tau), Lewy bodies (alpha-synuclein), mesial temporal sclerosis (MTS), argyrophilic grains (tau), co-existing TDP-43 pathology, and cerebrovascular disease.

Results: 44% of our cases required revision to their diagnosis. The most common diagnosis was FTLD-tau (36/52 or 69%, with 16 cases of Progressive Supranuclear palsy, 10 Corticobasal Degeneration, 8 Pick's, and 1 each of Argyrophilic grain disease and Globular Glial Inclusions). 16/52 (31%) were FTLD-TDP (9 Mackenzie type 1, 3 each of Mackenzie type 2 & 3 & 1 c9orf72). Co-existing neurodegenerative phenomena were common in our cohort with less than a third of cases being pure FTLD. The most frequent was MTS (present in 42%, especially older patients and those with FTLD-TDP Mackenzie type 1), while significant Alzheimer's pathology was seen in 26%, Lewy bodies in 19%, and Argyrophilic grains in 13.5%.

Conclusions: The relative frequency of each FTLD pathologic subtype in our cohort is comparable to other autopsy series from dementia clinics, and the 44% of cases requiring re-classification in our series is reflective of the rapidly evolving understanding of these disorders. Our series reports abundant co-existing neurodegenerative phenomena, which have often been overlooked in these patients historically, and our next step is to correlate the co-existing neurodegenerative phenomena with clinical symptomatology to determine whether their presence alters the clinical phenotype of FTLD.

1725 Somatostatin Receptor 2A: A Novel Immunohistochemical Marker of Meningioma

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Background: Meningiomas account for approximately one quarter of primary intracranial tumors, and while they generally display characteristic histologic features, there is some overlap with other tumors, such as schwannomas, hemangiopericytoma/solitary fibrous tumors, and gliomas. While epithelial membrane antigen (EMA), progesterone receptor (PR), CD99, bcl-2, and claudin-1 have been considered immunohistochemical markers of meningiomas, the reported sensitivities and specificities of these markers are not optimal. Based upon previously reported findings in a small number of cases, we wished to test the hypothesis that SST2A could prove to be a highy sensitive and specific marker of meningioma.

Design: 27 cases of meningiomas and 21 cases of schannomas, hemangiopericytoma/solitary fibrous tumors, or gliomas were obtained from the files of PhenoPath Laboratories and Consultoria em Pathologia. Deparaffinized, formalin fixed tissues were incubated with antibodies to SST2A [rabbit monoclonal antibody UMB1 (Epitomics, Burlingame, CA) with localization by the Quanto polymer based detection system (ThermoFisher, Waltham, MA)]. A semiquantitative scoring system was employed based upon the fraction of tumor cells showing positivity (low, <25% of tumor cells positive; intermediate, 26-75% of tumor cells positive; high, >75% of tumor cells positive).

Results: 27/27 (100%) of meningiomas were positive for expression of SST2A, virtually all of them strong and uniform (nearly 100% of tumor cells positive). In contrast, 2/21 non-meningiomas (both hemangiopericytoma/solitary fibrous tumors) demonstrated positivity, albeit focal. Thus, the sensitivity of SST2A for meningiomas was 100% with 90% specificity, based upon the limited tissues studied.

Conclusions: SST2A is one of two isoforms of the somatostatin 2 receptor, which in turn is one of five subtypes of somatostatin receptors. SST2A has been previously demonstrated to localize to neuroendocrine tumors, and has also been used as an immunohistochemical tissue correlate of in vitro I-[Tyr]-octreotide autoradiography. This study demonstrates an additional potential utility for SST2A, as we have demonstrated exceedingly high sensitivity and specificity for meningiomas in comparison to other tumors for which there can be histologic overlap. Further studies are warranted to see if this high sensitivity and specificity can be documented in a larger series of tumors, as well as many of the morphologic variants of meningiomas.

1726 Histology and Immunohistochemical Profile of Diffuse Intrinsic Pontine Glioma (DIPG)

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Background: Pediatric tumors of the CNS are the 2nd most common malignancy in children. In particular, DIPGs are aggressive tumors with poor prognosis and account for 10-25% of pediatric brain tumors. The majority are of astrocytic origin with an infiltrative pattern and localized to the Pons. The diagnosis of DIPG is based on the presentation on MRI, although distinction from primitive neuroectodermal tumors (PNETs) on imaging studies alone is difficult. Surgical treatment is often not possible due to the sensitive location. Treatment strategies have traditionally been limited to radiotherapy and chemotherapy, with very poor effectiveness. Most studies have shown median survival times of less than a year with 90% of children dying within 2 years.

Design: We built 2 multi-tissue arrays with 24 DIPG samples obtained from autopsy material, most patients had received prior radiation treatment. The mean age of patients at the time of death was 7.9 years with 38% female and 46% male. We analyzed morphology and expression of several proteins by immunohistochemistry, with the goal of identifying potential treatment targets and improving our understanding of the biology of these tumors.

Results: We analyzed the morphologic characteristics of 24 brainstem gliomas. The majority of the cases were high grade (22) with 17 cases having features of glioblastoma with pseudopalisading necrosis (14) and/or vascular proliferation (12), WHO grade IV and 5 cases with high grade features consistent with anaplastic astrocytoma, WHO grade III. One case was low grade (WHO grade II) and one case showed intermediate features between a grade II and grade III glioma. Microcalcifications were seen in 3 cases, 2 cases showed the presence of giant cells and gemistocytes were present in 2 other cases. The results for the different immunohistochemical markers were scored by 2 pathologists. The majority of the tumors were positive for GFAP (24/24), MIB1 (23/24), Olig2 (22/24), p16 (20/24), p53 (20/24), Sox2 (19/24), EGFR (16/24) and BMI1 (9/24).

Conclusions: Our results suggest that dysregulation of EGFR and p53 may play an important role in the development of a majority of DIPGs. A majority of the tumors express stem cell markers such as Sox2 and Olig2, consistent with a role for tumor stem cells in the origin and maintenance of these tumors. In conclusion, we have an excellent resource in which to study the morphologic diversity and protein expression of 24 DIPGs. These could aid in the identification of potential novel therapeutic and prognostic makers.

1727 Tumor-Infiltrating Lymphocytes in Glioblastoma Are Associated with Mutations in *NF1, RB1* and *TP53* and Enriched in the Mesenchymal Transcriptional Class

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Background: Tumor-infiltrating lymphocytes have prognostic significance in many human neoplasms and may be an important variable to consider in future immunologic therapies. Their biologic and clinical significance in glioblastoma (GBM) have not been fully defined. We investigated if lymphocytes in GBM were associated with specific molecular alterations, histologies or patient outcome.

Design: Using publicly available molecular, histologic and clinical data from The Cancer Genome Atlas (TCGA), we annotated lymphocytes as absent (0), present (1+), or abundant (2+) in 171 cases. Associations between lymphocytes and other histologic features, copy number alterations, mutations and gene expression class were examined by Chi-square tests. The association of lymphocytes with survival was assessed by log-rank tests.

Results: We detected a positive correlation between lymphocytes and GBMs with gemistocytes, sarcomatous cells, epithelioid cells, and giant cells (all $p<0.05$). Conversely, lymphocytes were depleted in GBMs characterized by small cells and oligodendroglial cells (both $p<0.05$). Lymphocytes were also negatively correlated

with EGFR-amplification ($p<0.05$). Lymphocytes were enriched in the mesenchymal transcriptional class ($p<0.05$), with 71% of cases in this class displaying abundant (2+) lymphocytes. Lymphocytes were also strongly associated with mutations in *NF1*, *TP53*, and *RB1* (all $p<0.05$), which are enriched in the mesenchymal transcriptional class and characteristic of gemistocytic, sarcomatous, epithelioid, and giant cell histologic subtypes of GBM. Within the mesenchymal transcriptional class, lymphocytes were associated with NF1 deletions ($p<0.05$). Lymphocytes were not associated with survival.
Conclusions: We found that tumor-infiltrating lymphocytes in GBM were strongly correlated with the mesenchymal transcriptional class; associated with mutations in *NF1*, *TP53*, and *RB1*; and typical of histologic subtypes of characterized by these mutations including gemistocytic, sarcomatous, epithelioid, and giant cell GBMs. Immunogenic mechanisms underlying these molecular and histologic associations remain to be determined.

1728 1p/19q Co-Deletion and Polysomy in Oligodendroglial Tumors – A Single Institution Study

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Background: The allelic loss of 1p and 19q in oligodendroglial tumors is mediated by the formation of the balanced translocation involving chromosomes 1 and 19 with subsequent loss of the derivative chromosome der (1; 19) (p10; q10) and maintenance of the der (1; 19) (q10; p10). While this observation and subsequent data has clearly shown a survival advantage and response to therapy in these tumors, the co-existence of the other changes such as polysomy and its outcomes have only been explored in very few studies. In this study we retrospectively analyzed the FISH patterns of 1p/19q co-deletion in oligodendroglial tumors.
Design: We collected pathological data and FISH results on oligodendroglial tumors during 2007 to 2010 from database of Pathology Department at Memorial Sloan-Kettering Cancer Center. Eighty-two patients with 1p/19q co-deletion were identified. There were 37 males and 45 females. Forty-eight cases were WHO Grade II oligodendrogliomas and thirty-four tumors were WHO grade III/anaplastic oligodendrogliomas.
Results: In this group of eighty-two 1p/19q co-deleted oligodendrogliomas, 17 cases showed in addition polysomy for 1p and/or19q (21%). Of the forty-eight WHO grade II tumors, 42 (87.5%) showed standard co-deletion (SCOD) and six showed co-deletion with polysomy (12.5%). Of the thirty-four WHO grade III tumors, 23 (68%) showed SCOD and eleven showed co-deletion with polysomy (32%).The mean age in both groups (Polysomy with co-deletion and SCOD) were 48 years and 42 years respectively. MGMT methylation was performed on thirty one patients. Sixteen out of 21 (76%) patients with SCOD showed MGMT methylation whereas all ten patients with co-deletion and polysomy showed MGMT methylation.
Conclusions: 1) In Oligodendrogliomas with co-deletion of 1p/19q, polysomy is seen in 20% of cases
2) Polysomy is seen 65% (11/17) of Grade III oligodendrogliomas as compared to 35% (6/17) in Grade II oligodendrogliomas.
3) The biological significance of these findings will be better understood with studies on a larger cohort of patients and clinical follow-up.

1729 Ras-MAPK Pathway Mutation Analysis in Cerebellopontine Angle Tumors

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Background: Activity in the RAS-mitogen associated protein kinase (MAPK) signaling pathway can be altered in neurofibromatoses type 1 (NF1) and 2 (NF2) where the loss of tumor suppressors can lead to elevated MAPK activity and tumorigenesis (e.g., bilateral vestibular schwannomas (VS) and meningioma in NF2). Alternatively, activating mutations in B-raf and/ or Ras components of the Ras-MAPK pathway can lead to increased mitogenic signaling. One recent investigation of nerve sheath tumors identified *BRAF* V600E and *KRAS* G12S mutations in sporadic schwannomas, particularly in the head and neck, including VS. The primary aim of this study was to assess the frequency of *BRAF* and *KRAS* activating mutations in sporadic, unilateral VS at the cerebellopontine angle (CPA). A secondary aim was to determine whether these mutations are identified in other CPA tumors in the differential diagnosis of VS.
Design: CPA and CPA region tumors, as well as meningiomas with prominent fibroblastic histology, were identified in the electronic medical record. Clinical history, as well as radiology and pathology reports, were reviewed to exclude patients with NF1/NF2. For selected cases, paraffin blocks were pulled and slides reviewed to verify the presence of sufficient tumor. Pyrosequencing (PS) of *BRAF* (exon 15, codon 600) and *KRAS* (exon 2, codons 12 and 13) was performed following PCR of DNA isolated from representative tissue sections.
Results: Eleven unilateral VSs (mean age 51.2 years, 7 males) and eleven comparison cases (mean age 54.1 years, 4 males) were identified. Comparison cases consisted of nine meningiomas (4 CPA, 6 with fibroblastic histology, 2 WHO Grade II) and two infratentorial hemangiopericytomas (WHO Grade II). No *KRAS* mutations were identified. Two cases demonstrated *BRAF* codon 600 T>A sequence changes at or just above (3 and 4 % in a single VS and hemangiopericytoma, respectively) the analytical sensitivity threshold of our clinical PS assay (set at 3%).
Conclusions: Very low levels of mutant *BRAF* sequence were identified in two cases (1 VS, 1 hemangiopericytoma), possibly representing a minor clone in these cases. These changes, potentially detectable by PS, would be below the detection of typical Sanger sequencing methods. Moreover, *KRAS* codon 12 or 13 mutations were not identified. Thus, recently reported *BRAF* and *KRAS* mutations in sporadic VSs are likely to be very rare events and likely noncontributory in the differential of CPA tumors. Alternate mechanisms to Ras-MAPK signaling pathway activation, or other pathways of oncogenesis, may be more common in sporadic non-syndromic VS.

1730 Insular Low Grade Gliomas (LGG): The Role of Molecular Markers and Extent of Surgical Resection (EOR)

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Background: Insular gliomas represent the 25% of all Low Grade Gliomas (LGG) and are a surgical challenge for anatomo-functional reasons. The achievement of a radical resection is limited by their attitude to infiltrate the eloquent cortical areas and functional subcortical pathways. The role of EOR of insular gliomas on overall survival (OS) has been recently demonstrated, while the impact of the molecular profile in these lesions has not been investigated up to now.
Design: A cohort of consecutive 34 patients, resected for insular LGG, were retrospectively investigated from a molecular and volumetric point of view. Formalin fixed and paraffin embedded tissues were analysed for p53, 1p19q deletion, IDH1/IDH2 gene status and MGMT promoter methylation. Histologic and grade evaluation were performed according to WHO classification. The EOR was computed by analyzing pre- and post-operative T2-weighted MRI images.
Results: Patients were histologically classified as follows: astrocytomas, oligodendrogliomas and mixed oligoastrocytomas in 58.8%, 11.8% and 29.4% of cases respectively. A positive immunohistochemistry expression of p53 was observed in 61.8% of cases, while IDH1 mutation was found in 85.3% of cases (R132H and R132G mutations). All cases were wild-type for IDH2. MGMT promoter resulted methylated in 73.5% of patients and 1p/19q codeletion was demonstrated in 35.3% of samples. The mean EOR was 85% (54-100). Histological subtype ($p<0.001$), EOR ($p<0.002$) and 1p/19q codeletion ($p<0.014$) were demonstrated to be associated with OS at univariate statistical analysis. EOR has been proved to be the strongest independent predictive factor of OS by multivariate analysis ($p=0.048$). In 12 patients a second surgery for tumoral progression has been performed. In these cases, the molecular profile was similar to that of patients without tumoral recurrence. However the absence of 1p/19q codeletion was associated to a higher risk of recurrence ($p=0.02$).
Conclusions: The present investigation strengthened the prognostic value of EOR on OS. Biomarkers expression confirmed literature data on LGG, suggesting that insular LGG are not characterized by a specific molecular profile. OS was not significantly influenced by molecular markers even though absence of 1p/19q codeletion has been proved to be more associated to the risk of tumor recurrence.

1731 Autopsy Bias Adjustment for Factors Associated with Cortical Beta-Amyloid Deposition

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Background: In studies involving the nervous system (e.g. Alzheimer's disease), the outcome of interest is often assessed from deceased participants who undergo autopsy (the autopsy sample). The autopsy sample is not a true random sample from the target population and is often affected by potential selection mechanisms. Therefore, estimates of association between a risk factor and outcome within the autopsy sample may not accurately represent the situation in the target population, resulting in autopsy bias. Objectives of this study are to describe a method for adjustment of autopsy bias and to demonstrate application of the method using an autopsy based study.
Design: Histological sections from four regions of the brain for 231 autopsied participants of the Honolulu-Asia Aging Study (HAAS) were examined to determine extent of beta-amyloid deposition. Associations of selected risk factors with beta amyloid deposition were examined with and without adjustment for autopsy bias. Autopsy bias adjustment was accomplished first by developing probability of selection into the autopsy sample using demographic and life style variables and then estimating autopsy bias adjusted measures of association using the inverse probability of selection as weights.
Results: Adjustment for autopsy bias affected both the statistical significance and magnitude of the odds ratio for some risk factors. For example, age, years of education and waist circumference were all significantly associated with beta amyloid deposition following yet not before adjustment for autopsy bias. Other risk factors although significantly associated with beta amyloid deposition, showed substantial change in the magnitude of the odds ratio following adjustment. For example, those with coronary heart disease (CHD) were nearly 4 times more likely to have extensive beta amyloid deposition compared to those who had no CHD (OR=4.096, $p=0.0085$), but after adjustment for autopsy bias the comparable odds ratio was reduced (OR=2.781, $p=0.0232$).
Conclusions: Adjustment for autopsy bias may affect both the magnitude and statistical significance of the measure of association. The key in adjusting for autopsy bias is developing the selection model using a sufficient set of factors that influence the selection mechanism. In the absence of adjustment for autopsy bias, interpretation of results from autopsy studies pertain only to the population of autopsied individuals.

1732 The Utility of Immunohistochemical Markers for the Differential Diagnosis of Metastatic Melanoma in the Central Nervous System

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Background: Some melanomas metastatic to the central nervous system (CNS) pose little diagnostic difficulty while many others are challenging due to ambiguous histological and immunohistochemical features. In such cases, aberrant

immunohistochemical staining results complicate differential diagnosis. In order to determine the most appropriate immunohistochemical panel for diagnosis, we analyzed immunohistochemical features of CNS metastatic melanomas.
Design: We included 48 patients with CNS metastatic melanomas (31 male, 17 female; median age= 57) from a total of 77 patients identified from a database search. All cases were immunostained with S100, EMA, Sox-2, Sox-10, CAM5.2, O13, Melan-A, HMB45 and MITF by using tissue microarray.
Results: Twenty seven tumors harbored melanin pigment, while 21 were amelanotic. Metastatic melanomas were positive for S-100 protein(98%), Sox-10(96%), HMB45(88%), Melan-A(79%), MITF(77%) and Sox-2(54%). MITF immunostaining was weak in one-third the cases in which this antibody was positive. Interestingly, we found convincing EMA positivity in 6 (13%), and 013 positivity in 2 (4%) of the cases. All tumors were negative for CAM 5.2. There was a positive association between HMB45 immunostaining and presence of melanin pigment (p=0.037).
Conclusions: Among individual markers, S-100 protein and Sox-10 appear the most sensitive but least specific since other entities have similar staining patterns. However, since 100% of our cases were positive for either of these stains, negative staining in both markers appears incompatible with the diagnosis of metastatic melanoma. The staining for Sox-2 poses significant diagnostic difficulty since most malignant gliomas are also positive with this antibody. Rare positivity with EMA and O13 are also confounding, and the weak staining with MITF can pose difficulties in the interpretation. Finally, stain for HMB45 may not be necessary if the tumor does not harbor pigment on H&E evaluation.

1733 Lack of Human Cytomegalovirus in Gliomas. A Viral Load Analysis by Quantitative Real Time–PCR

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Background: Recently, a consensus has been reached that there is sufficient evidence to conclude that human cytomegalovirus (HCMV) sequences and viral gene expression exist in most, if not all, malignant gliomas. However, no previous report has approached a quantitative analysis of the HCMV in gliomas. We aimed to study the HCMV viral load in different stages of human primary gliomas.
Design: A total of 82 paraffin embedded tissues of human primary gliomas (stages II: 15; III: 13 and IV: 54) from the Elche & Alicante Hospital Biobanks were included in this study. DNA was isolated using a high performance forensic kit (QIAamp DNA Investigator; Qiagen). HCMV was analyzed by Real Time PCR using a standardized kit for HCMV quantitation in diagnostic (*RealStar CMV PCR Kit 1.0; **Altona DIAGNOSTICS***). Positive and negative controls were included. Each DNA sample was tested in triplicate.
Results: A six points standard curve (Pearson's correlation coefficient >0.99) was used to interpolate the HCMV viral load from 10 to 10.000 copies, unexpectedly 79 samples of this serie of gliomas showed undetectable DNA of HCMV. Three cases showed a low number of viral copies (<10) (stages III: 2; IV: 1). The strength of the analytical accuracy components required to characterize a quantitative test (trueness, precision and limit of detection) is assured by the employed methodology. The controversy regarding the existence and role of HCMV in gliomas has been debated in the literature. The recent consensus pointing to an important role of HCMV in gliomas needs to be reviewed.
Conclusions: Our results strongly support that HCMV is nearly absent in gliomas. The role of HCMV infection in glioma development is irrelevant.

1734 Cerebrovascular A-beta Amyloid in Surgical Specimens: Clinicopathological Correlates

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Background: The spectrum of CNS vascular A-beta amyloid includes cerebral amyloid angiopathy (CAA), with media/adventitia A-beta deposits in small/medium size cortical and leptomeningeal arteries; A-beta-related angiitis (ABRA), with angiodestructive often granulomatous inflammation (Brain 2005;128:500-15); and CAA-related inflammation (CAA-RI), in which inflammation with giant cell reaction surrounds amyloid-laden vessels without angiodestructive features (Ann Neurol 2004;55:250-6).
Design: CNS biopsies from 62 patients with confirmed A-beta amyloid angiopathy (Surgical pathology archive 1987-2011) were re-reviewed for the presence, location and extent of vascular: A-beta deposits (leptomeningeal/cortical;intimal/medial/adventitial; segmental/circumferential); inflammation (lymphocytes/macrophages/giant cells; perivascular/transmural); and fibrinoid necrosis. Following strict pathological criteria they were classified as ABRA, CAA or CAA-RI. Clinical and imaging data were collected from the medical records.
Results: Clinical data at presentation for ABRA, CAA, CAA-RI and overall group are summarized in the Table

	ABRA (N=21)	CAA (N=32)	CAA-RI (N=9)	Total (N=62)
Male	11 (52%)	15 (47%)	5 (56%)	31 (50%)
Female	10 (48%)	17 (53%)	4 (44%)	31 (50 %)
Age (Median, range)	67 (42-84)	72 (48-86)	72 (53-79)	70.5 (42-86)
Intracranial hemorrhage	1 (5%)	23 (72%)	2 (22%)	12 (19%)
Altered cognition	5 (24%)	6 (19%)	2 (22%)	13 (21%)
Seizure or Headache	11 (52%)	3 (9%)	4 (44%)	18 (30%)

Reason for/ time of biopsy was hematoma evacuation in 1 (5%) ABRA, 22 (69%) CAA and 2 (22%) CAA-RI. A mass lesion was present in 7 (33%) ABRA, 4 (12%) CAA and 2 (22%) CAA-RI; leptomeningeal enhancement in 9 (43%) ABRA, 2 (6%) CAA and 3 (33%) CAA-RI. At last follow up a poor outcome (Death or Rankin Score 4+) was noted in 29% of patients with ABRA, 75% with CAA, and 56% with CAA-RI.
Conclusions: CAA, ABRA and CAA-RI occur within a wide age range. As previously observed, CAA presents most often with intracranial hemorrhage. ABRA and CAA-RI likely represent a spectrum of one clinicopathological entity.

1735 a-Synuclein in the Mucosa of the Human Vermiform Appendix

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Background: Aggregation of α-synuclein (α-syn) in Parkinson's disease (PD) has been hypothesised to begin in the olfactory bulb and the enteric nervous system (ENS) before propagating to the central nervous system. It is still unknown where exactly ENS pathology may begin. The aim of this study was to evaluate the distribution of normal and aberrantly phosphorylated (Ser129) α-syn within the human gastrointestinal tract.
Design: Archival tissues were obtained from patients with no history of synucleinopathy. Intestinal tissue was retrieved from 5 patients who underwent right hemicolectomy for carcinoma resection (average age = 76, range= 67-90). Gastric tissue comes from 5 different patients who received subtotal gastrectomy for various reasons (average age= 61, range=56-70). Relative α-syn expression in tissues was determined by IHC. Identity of α-syn stained structures was determined by immunofluorescence double-labeling.
Results: Vermiform appendix is easily distinguished from other tissue by the plentiful nerve fibres of the mucosal plexus in the lamina propria which exihibit strong α-syn staining. Within the mucosal plexus of the appendix, there is further differential staining with a fine reticular pattern in the apical lamina propria representing the villus subplexus and denser basal staining in the pericryptal and external lamina subplexus. The laminae propriae of the stomach, terminal ileum and colon exhibit only rare α-syn positive nerve fibres. Inclusions of phosphorylated Ser129 α-syn are noted in the mucosa of all appendices examined and were also present in submucosal and myenteric ganglia.
Conclusions: α-syn positive nerve fibres are abundant in the lamina propria of the vermiform appendix, contrasting with the relative scarcity in the stomach, terminal ileum and colon. This holds implications for the initiation of α-syn aggregation in the ENS and possibly the pathogenesis of PD. Given the large immune component of the vermiform appendix, this may provide support for immune-related hypotheses of PD etiology.

1736 The Expression of Progenitor Cell Markers in Primary Central Nervous System Lymphoma: Role of SOX2/OCT4 in Lymphomas with B-Cell Phenotype

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Background: Primary central nervous system lymphoma (PCNSL) is typically a diffuse large B-cell lymphoma (DLBCL) and factors associated with its prognosis have not been clearly identified. In recent studies, SOX2-OCT4 pathway has been found to be highly active in cancers of the prostate, stomach, breast, colon, brain and testis and most of these reports focus on the correlation between SOX2 expression and various clinicopathological parameters. To the best of our knowledge, the role of SOX2-OCT4 pathway in the biology of DLBCL is not clear and SOX2/OCT4 expression have not been studied in PCNSL. Based on recent studies on CNS neoplasia, we have hypothesized that SOX2-OCT4 pathway may be active in PCNSL.
Design: We reviewed all patients with DLBCL of the CNS diagnosed at our institution during the last 15 years. All available specimens were stained with CD10, Bcl6 and MUM1 to evaluate DLBCL subtype and with SOX2 and OCT4 using commercially available antibodies. The results were analyzed in the light of clinical features.
Results: We included 115 patients in the study. Seventy patients (37 male, 33 female) had DLBCL with no evidence of systemic involvement or immunosuppression and were considered in the PCNSL category. Eighteen patients had HIV/AIDS (15 male, 3 female) and were included in the HIV category. Five patients (1 male, 4 females) had monomorphic B-cell post-transplant lymphoproliferative disorder. The remaining 22 patients (9 males, 13 females) had systemic DLBCL with secondary CNS involvement. Immunophenotypic profiling performed in 32 cases (16 PCNSL, 7 HIV, 9 systemic,) revealed that 23 non-germinal centre and 9 germinal centre type. Almost all cases stained with the SOX2 antibody (>95%) showed diffuse strong nuclear positivity and rare tumors (<10%) in the germinal center type demonstrated strong OCT4 positivity.
Conclusions: This study provides preliminary evidence that the SOX2-OCT4 pathway may be involved in DLBCL of the CNS. While the practical implications and the diagnostic utility of this staining pattern remains to be determined, the strong SOX2 positivity along with only rare OCT4 positive cases imply that SOX2/OCT4 may be altered in DLBCL and this alteration may involve different mechanisms. This is particularly interesting in the light of earlier studies that demonstrate expression of SOX2 to be inversely related to normal hematogenic potency.

1737 Protein Arginine Methyltransferase 5 Is Highly Expressed in Glioblastoma and Important for the Growth of Glioma Cells

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Background: Protein Arginine Methytransferase 5 (PRMT5) is a type II protein arginine methyltranferase that catalyzes transfer of methyl groups from S-adenosyl methionine to the arginine residues on histones or non-histone proteins. PRMT5 is involved in a variety of biological processes such as transcriptional regulation, RNA splicing and signal transduction. Recent studies demonstrate that PRMT5 is highly expressed in some types of tumor cells including leukemia, colon, lung and prostate cancer and may serve an important functional role. However, the expression of PRMT5 in astrocytomas and the role of PRMT5 in tumor progression have not been investigated.
Design: We performed PRMT5 immunostaining on paraffin blocks of 20 cases of astrocytomas of different grades (10 glioblastoma, 5 WHO II diffuse astrocytoma, 5

anaplastic astrocytoma, and on 10 epilepsy brains. The intensity (0-3) and percentage of tumor cell staining were multiplied to determine an H-score. In addition, we knocked down the expression PRMT5 in glioma cell lines and determined the effect on cell growth.
Results: PRMT5 was undetectable in astrocyte while expressed in neuron of control brain sections. The expression of PRMT5 was undetectable in WHO II astrocytomas as well. However, the expression of PRMT5 was significantly higher in high grade astrocytomas ($p<0.001$). Among high grade astrocytomas, PRMT5 expression was significantly higher in glioblastoma than in anaplastic astrocytoma ($p<0.001$). Interestingly, PRMT5 immunostaining appears heterogeneous throughout the tumor tissues and has a predominantly nuclear positivity in GBM cells. Furthermore, upregulated cytoplasmic expression of PRMT5 was identified in the endothelial cells of the microvasculature in glioblastoma. Knocking down of PRMT5 in U251 and LN229 significantly inhibited cancer cell growth.
Conclusions: PRMT5 is important for glioma cell growth and may be a marker of malignancy in tumors of glial origin.

1738 Factors Associated with Survival in Patients with Breast Cancer (BC) Brain Metastasis (BM)

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Background: Up to 15% of patients with stage IV BC will eventually develop BM in the course of their disease, which has become a major clinical problem due to the limited effective systemic therapies. This substantiates the urgent need for better understanding of risk factors for developing BM to obtain the largest benefit from prevention and to utilize optimal treatment strategies. The aim of study was to determine the clinicopathologic factors significantly associated with survival in these patients.
Design: We analyzed all BC patients with BM from 1997 to 2012 at our institution. The clinicopathologic factors were recorded, including age, race, tumor type, histologic grade, receptor status, stage at diagnosis and presence of other organ metastases to identify factors significant for overall survival (OS), BM free survival (BMFS) and post BM survival (PBMS) by utilizing the Cox proportional hazard model.
Results: Of all patients with stage IV BC in the study period, 88 had BM at diagnosis (6) or subsequently (82). There were significantly higher proportions of HER2 subtype (25%) and triple-negative (TN) BC (26%) among these patients compared to the general BC population. High grade and stage IV at diagnosis were significantly associated with poor OS by univariate analysis, and the former remained significant in multivariate analysis ($p<0.01$). Lobular BC, high grade, stage IV at diagnosis and non-luminal subtypes were significantly associated with BMFS by univariate and multivariate analysis ($p=0.01$, 0.02, <0.0001 and <0.01, respectively), whereas BMFS did not differ significantly between HER2 and TNBCs. The mean BMFS of the three BC subtypes were 36.5, 28.4 and 30 months, respectively. While histologic grade, the presence of other organ metastasis and BC subtype were significantly associated with PBMS by univariate analysis, only histologic grade remained significant in multivariate analysis ($p=0.02$).
Conclusions: While histologic grade was universally associated with survival in BC patients with BM, BMFS differed significantly between tumor types, stage at diagnosis and BC subtypes. In addition to TNBC, a known risk factor of developing BM, HER2 subtype showed a similar incidence of BM and BMFS, likely reflecting that HER2 targeted therapy improves systemic disease control while unmasking BM in these patients. The lack of significance in OS by other factors is likely due to relatively shorter follow-up in a significant proportion of the patients. Nonetheless, this analysis might help in stratifying patients into prognostically significant categories for optimal treatment decision making.

1739 Utility of Steroidogenic Factor-1 in the Pathologic Evaluation of Clinically Non-Functioning Pituitary Adenomas

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Background: Approximately 30% of the pituitary adenomas are clinically non-functioning and some are negative with the routine hormone stains. Recent studies showed that novel transcription factors such as steroidogenic factor-1 (SF1) can be positive when hormonal stains are negative and may better classify adenomas. However, except for rare reference laboratories and academic centers, SF1 is not widely used or preferred for the work up of pituitary adenomas. The purpose of our study is demonstrate the utility of SF1 in classifying pituitary adenomas and to characterize the clinicopathological features of clinically silent SF1 positive adenomas.
Design: We reviewed all pituitary adenomas diagnosed at our institution over a 5 year period and selected all clinically non-functioning cases that were negative in routine hormonal stains and had sufficient material. The results were analyzed to determine features that may distinguish SF1 positive adenomas from those that are SF1 negative.
Results: Based on the inclusion criteria, we identified 86 tumors (59 male, 27 female) for the study. 27 of these were SF1 positive. The median age for the SF1 positive group was 52 years and all tumors were macroadenomas. There was only one atypical adenoma in the SF1 negative group. There was no difference between SF1 negative and SF1 positive adenomas regarding the gender distribution, age, tumor volume, histological growth pattern, bone or sinus invasion, mitoses, Ki67 labeling index or recurrence/progression rate.
Conclusions: Silent gonadotroph adenomas constitute a significant portion of clinically non-functioning pituitary adenomas and there are no clinical or pathological features that can distinguish them without the use of SF1 stain. Routine use of SF1 staining should be considered as a part of pathological evaluation of these tumors and leads to more accurate classification.

1740 Uncommon Focal/Regional Heterozygous or Homozygous Deletion of *SMARCB1* (hSNF5/INI1) Locus in Two Atypical Teratoid/Rhabdoid Tumors

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Background: Atypical teratoid/rhabdoid tumors (ATRTs) are high grade tumors with CNS and non-CNS presentations. They comprise 1-2% of pediatric brain tumors, occurring most often in infancy. While characteristic histology of ATRTs is rhabdoid cells with abundant eosinophilic cytoplasm, they vary in histologic appearance and can mimic many other malignancies. Inactivation of the hSNF5/INI1 (*SMARCB1*) tumor suppressor gene, a component of the SWI/SNF chromatin-remodeling complex, is the characteristic genetic alteration in > 95% of ATRTs. It is associated with loss of nuclear immunostaining for INI1 (BAF-47). Several cases have now been reported with alternative alterations in the *SMARCA4* (BRG1) gene, another component of the SWI/SNF complex. We present two cases of ATRT with heterogeneous staining for INI1, with an uncommon pattern of focal/regional heterogeneous or homozygous deletion of the hSNF5/INI1 locus demonstrated by fluorescence in situ hybridization (FISH).
Design: The study group is comprised of 2 cases. The first is a 3-month old with a metastatic lesion of the lower lip received in consultation because of heterogenous staining for INI1. The second case is a large, complex solid and cystic, congenital right frontal lobe mass in a 5-day old twin. Tumor tissue was paraffin-embedded, formalin-fixed, and stained with H&E. Immunohistochemical staining for INI1 was performed using an anti-BAF-47 antibody. FISH was performed using a cocktail of hSNF5-specific locus probes with chromosome 22-specific reference probes.
Results: Both tumors contained regions of rhabdoid cells histologically characteristic for ATRTs. Both cases also showed heterogeneous immunostaining for INI1, with regions of tumor cells with intact nuclear positivity for INI1 interdigitating with and adjacent to regions with loss of nuclear INI1 staining. Repeat INI1 staining showed similar results. FISH demonstrated an uncommon pattern of focal/regional homozygous deletion of the hSNF5/INI1 locus in case 1, while case 2 showed regional heterozygous deletion of the hSNF5/INI1 locus.
Conclusions: These two cases show an unusual pattern of deletion of the *SMARCB1* locus associated with a heterogeneous loss of nuclear INI1 immunostaining. We are not aware of a previous report of this observation. These cases represent the first report of inherent molecular heterogeneity for *SMARCB1* deletion within tumors that otherwise have classic histologic features for ATRT.

1741 MicroRNA, MGMT Methylation and PTEN & P53 Mutations in Glioblastomas

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Background: Glioblastoma is the most common and malignant intrinsic brain tumor. Because of its extremely unfavorable prognosis, it is important to develop more effective diagnostic and therapeutic strategies based on biological and clinical sub classification system. Genomic profiling and miRNA expression profiling have suggested the existence of multiple glioblastoma subclasses,although their number and characteristics vary among studies.
Design: We analyzed microRNA expression profiles using the mirCURY LNA TM microRNA Arrays platform in 33 glioblastomas multiformes. All cases were studied at diagnosis, the median age was 66 years and the most frequent localization was temporal (40%).The median overall survival was 10 months. The promoter status of MGMT was determined by MLPA. By direct sequencing PTEN, EFGR and P53 mutations were analyzed. FISH for PTEN and EFGR was also evaluated. After extraction, microRNAS were labeled with Hy3TM/Hy5TM fluorescent label using the miRCURYTM LNA Array labeling kit (Exiqon, Denmark) and hybridized to the miRCURYTM LNA array v8.0. The hybridization and wash steps were performed according to the miRCURYTM LNA array manual in a Tecan HS 4800 ProTM hyb (Tecan, Austria). Scanning was performed in a Genepix 4000B scanner (Axon Instruments). The quantified fluorescence intensities were normalized using the global LOWESS.
Results: We found that miR-483-3p is overexpressed in 15% of GBM. Hsa-mir-483 is located within intron 2 of the IGF2 locus in 11p15. In 10% of cases Hsa-miR-541, Hsa-miR-621 and Hsa-miR-218, located in 14q32, 13q14.11, and 5q34 respectively, are overexpressed. MGMT hypermethylation was evaluated in 22 cases, and MGMT hypermethylation was detected in 7 cases (32%). A supervised analysis by SAM showed differential expression (FDR<0,005). Thus nmu-mir718 was downregulated in hypermethylated cases, while hsa-miR50* and hsa-mir 483-3p were up-regulated in moderate or absence of methylathion. The mutational analysis of PTEN and P53 genes showed differential expression between mutated and wild type cases, in about 50 microRNA. Regarding PTEN deletion, we also observed differential profiles.
Conclusions: MicroRNA expression helps to define clinically and genetically distinct glioblastoma subclasses. The use of a classification system may aid in the selection of subclass-specific therapies that will improve outcome for glioblastoma patients.

1742 Analysis of *IDH* Mutation, 1p19q Deletion, and *PTEN* Loss in Low Grade Diffuse Gliomas

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Background: Astrocytomas grade II and III have unpredictable rates of biological and clinical progression, making management decisions difficult. Currently, several clinical and radiological characteristics are utilized to predict progression and survival, but collectively are suboptimal.

Design: In our study, we analyzed a large set of non-enhancing hemispheric grade II-II gliomas for *IDH* mutations (*mIDH*), 1p19q co-deletion, *PTEN* deletion, and *EGFR* amplification to determine if these singly or in combination offer advantages over tumor grading for prediction of overall survival (OS) and /or progression free survival (PFS).

Results: In this cohort, neither pathologic diagnosis nor gradewere predictive of OS or PFS. The greatest individual predictor was *mIDH* when both immunohistochemical and sequencing based assays were considered. *mIDH* was a predictor of longer OS and PFS for the entire group of tumours. 1p19q deletion alone was predictive of OS but not of PFS. With multifactorial analysis, Pathology again was not a significant predictor of OS or PFS. However, *mIDH*, 1p19 deletion, and, *PTEN* deletion were all found to be significant variables. Use of Cox regression analysis to construct groups of high and low risk based on *IDH*, 1p19q, and *PTEN* status resulted in a model with greatest predictive value for OS and PFS.

Conclusions: This data leads us to conclude that this combination of tests may be particularly effective in discriminating good prognosis from poor prognosis hemispheric gliomas. We would further propose that such a scheme merits testing on larger prospective cohorts. Should such confirm our findings, routine clinical analysis of hemispheric gliomas for *mIDH*, 1p 19q co-deletion and *PTEN* loss would be justified.

1743 Enhancer of Zeste Homologue 2 (EZH2) Expression Is Associated with Cell Proliferation in Medulloblastoma

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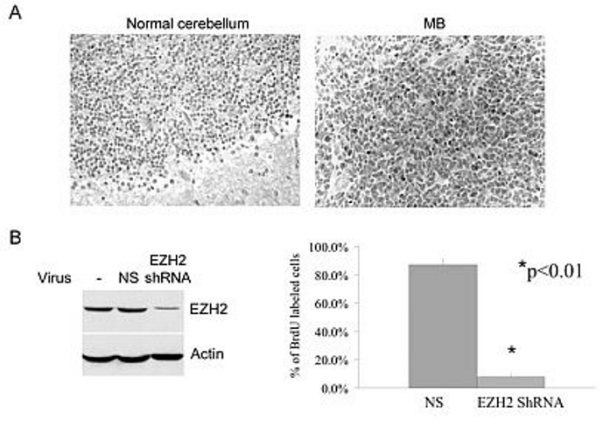
Background: A failure in control of proliferation of cerebellar granule neural progenitors (CGNPs) is thought to lead to medulloblastoma (MB), the most common malignant brain tumor in children. The molecular events associated with the development of MB are not fully understood. EZH2 is a member of the polycomb group family of proteins important for transcriptional regulation. EZH2 expression is associated with high proliferation and aggressive behavior in cancers. In this study, we investigated the expression of EZH2 and its relationship with cell proliferation in human MB and during CGNP development in mice.

Design: Eighteen MB cases were examined by immunohistochemistry for EZH2 and Ki-67 proliferative index. Since normal mouse CGN development has been shown to recapitulate MB, EZH2 expression and functional assay were investigated in early postnatal cerebellum of CD1 mice. EZH2 expression was examined by immunohistochemistry. After knockdown of EZH2 expression using a lentiviral vector shRNA approach, we performed BrdU incorporation assay to determine whether EZH2 knockdown impaired CGNP proliferation.

Results: EZH2 nuclear staining was identified in all 18 MB cases whereas normal cerebellar tissue surrounding the tumor or normal mature cerebellum had no EZH2 expression (Fig1A). Fifteen cases (83%) showed moderate to strong EZH2 expression and 3 cases (17%) exhibited weak expression. Ki-67 proliferative indices were significantly higher in cases with moderate to strong EZH2 expression (mean=42%) compared to those with weak EZH2 expression (mean=8%) ($P < 0.05$), suggesting that EZH2 expression in MB is closely associated with tumor cell proliferation. EZH2 was highly expressed in the CGNPs in postnatal day 6 mice. When stable EZH2 knockdown was achieved in this model, the BrdU incorporation assay showed significant suppression of the proliferation of CGNPs in comparison to non-siliencing control (NS) (Fig1B).



Conclusions: EZH2 is highly expressed in MB and appears to play a major role in controlling tumor cell proliferation. These findings suggest that EZH2 could potentially be an important therapeutic target for MB.

1744 Pathologic Findings in Radiographic Nonlesional Pharmacoresistent Epilepsy

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Background: A subset of patients with pharmacoresistent epilepsy have no clear lesion on magnetic resonance imaging (MRI) i.e. nonlesional. There are limited descriptions of the histologic findings associated with such cases. This study retrospectively reviews a series of nonlesional patients to examine the pathology observed in these cases.

Design: 94 patients (74 adults and 20 pediatric) with chronic epilepsy and nonlesional imaging per standardized epilepsy imaging protocol from 2002-2011 were identified and histology slides from tissue resections were reviewed to document pathologic findings. Focal cortical dysplasia (FCD) was classified according to Palmini et al (Neurology 2004;62(Suppl 3):S2-8) and ILAE (Epilepsia 2010;51:676-685) criteria.

Results: Surgery included 67 temporal lobe resections, 26 extratemporal resections and 1 multilobar resection. Of the specimens received, subtotal submission occurred in 57.4% (N=54) and total submission occurred in 42.6% (N=40). Collectively, the most common findings were FCD (45%; N=42), gliosis (38%, N=36), hippocampal sclerosis (HS) (12%; N=11), and absent pathologic abnormalities (7%; N=7). Dual pathology (FCD and HS) was seen in 2 of these FCD cases. Among the 42 cases of FCD, most (71.4%; N=30) were Palmini et al type IA lesions with less frequently observed patterns being type IB (21.4%; N=9) and type IIB (7.1%; N=3). Corresponding ILAE classification for FCD included Ic (67%; N=28), type Ib (21%; N=9), type IIb (7%; N=3) and type IIIa (5%; N=2). The frequency of observed FCD was greater among the extratemporal lobe cases (69%) versus temporal lobe cases (34%). Adult and pediatric groups had comparable proportions of FCD cases. Of the cases with either isolated gliosis or no pathologic findings, 44% (N=18) were subtotal submissions and 56% (N=23) were total submissions.

Conclusions: FCD type I and HS are among the most common observed pathologic abnormalities in nonlesional chronic epilepsy cases. Slightly less than half of nonlesional cases show nonspecific gliosis or no obvious light microscopic abnormality; this may be a bit high due to incomplete histologic sampling of resected tissues in some cases.

1745 Inhibition of ATF5 Sensitizes Glioblastoma Cells to the Cytotoxic Effects of TNF-Related Apoptosis Inducing-Ligand (TRAIL) in a CHOP-DR5 Dependent Manner

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Background: Glioblastoma, the most common primary brain tumor, is a devastating disease with a dismal prognosis. Recent research has shown that glioblastomas reveal high-expression of the Activating transcription factor 5 (ATF5), whereas non-neoplastic astrocytes and mature neuronal cells are devoid of ATF5 expression. Therefore, ATF5 represents a viable treatment target for glioblastoma. Here, we provide a novel mechanism of how interference with the ATF5 pathway induces a cellular stress response in glioblastoma cells and in turn can be utilized for a combinatorial treatment involving TRAIL.

Design: Glioblastoma cells (U87 and LN229) were transfected with a dominant negative form of ATF5 or the respective control plasmid. Subsequently, cells were treated with suboptimal concentrations of TRAIL. Cell death was analyzed by counting of apoptotic nuclei, using fluorescence microscopy. Western blots were performed to determine caspase cleavage (activation) and protein expression of CHOP and DR5.

Results: Glioblastoma cells treated with suboptimal dosages of TRAIL or a dominant-negative form of ATF5 (d/n-ATF5) reveal only minimal apoptosis induction after 24 hours of treatment. However, combining d/n-ATF5 with TRAIL causes nuclear fragmentation and cleavage (activation) of caspases in glioblastoma cell lines, indicative of rapid apoptosis. This combinatorial treatment approach appears independent of *TP53* mutation status since both mutated and wild-type p53 cell lines responded to the combinatorial treatment regimen. Mechanistically, inhibition of ATF5 elicits an up-regulation of the stress response transcription factor, CHOP, coupled with an increase of DR5 protein levels. To clarify the role of CHOP in this pathway, CHOP protein levels were suppressed by a specific siRNA in glioma cells. Compared to glioma cells transfected with a non-targeting siRNA, cells with suppressed CHOP levels partially reversed the apoptotic effects of the combination treatment, consisting of TRAIL and d/n-ATF5. Mechanistically, siRNA mediated suppression of CHOP attenuated d/n-ATF5 driven DR5 up-regulation, suggesting that inhibition of ATF5 results in an enhancement of the extrinsic apoptotic cascade by elevating TRAIL receptors (DR5 levels).

Conclusions: Targeting the transcription factor ATF5 can be utilized to overcome TRAIL-resistance in glioblastoma cells.

1746 Utility of Olig2 and Notch-1 Immunostains in Glioblastomas in a Routine Histopathology Setting

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Background: High-grade gliomas are nearly uniformly fatal and have a dismal prognosis. Recent studies have identified subclasses of high-grade gliomas by molecular arrays. One subclass, referred to as the Proneural phenotype, carries prognostic and therapeutic significance. This phenotype correlates with longer survival and may predict response to Notch inhibitors. To date, only gene expression profiling is able to reliably subclassify glioblastomas (GBMs); development of simple assays that can be adopted to a routine histopathology setting are thus desirable. In this study, we test two immunohistochemical stains for their utility in glioblastomas in a clinical laboratory setting.

Design: Forty cases of newly diagnosed resected glioblastomas from 2005 at the Hospital of the University of Pennsylvania are included in this study. To test these cases, antibodies to Olig2 and Notch-1 are initially considered. The staining pattern

is scored semi-quantitatively as minimal (0), mild (1), mild/moderate (1.5), moderate (2), or strong (3) for both of these immunostains. Only nuclear staining is considered. Cases that are predominately positive for Olig2 and Notch-1 are expected to belong to the Proneural subclass. As such, cases with increased Olig2 and Notch-1 staining are assigned a Proneural phenotype. Kaplan-Meier analysis is performed to study survival of this subclass. Additionally, overall survival as a function of strength of staining is analyzed for each immunostain.

Results: Cases of glioblastomas demonstrated variable staining with both Olig2 and Notch-1 immunostains. There was a trend towards longer median survival with stronger Olig2 staining and stronger Notch-1 staining; however, these trends did not reach statistical significance. Cases with strong Olig2 staining had a median survival of 73.6 weeks vs 47.3 weeks. Cases with only minimal or mild Notch-1 staining had a median survival of 24.4 weeks vs 56.4 weeks. The overall median survival was 48.3 weeks.

Conclusions: 1. Stains to Olig2 and Notch-1 may be adopted in a clinical setting to test glioblastomas by IHC.

2. Increased Olig2 and Notch-1 staining trended towards improved survival of glioblastomas in this study. However, immunohistochemistry with these markers alone is not able to reliably subclassify GBMs.

3. Further studies should be considered to subclassify GBMs with additional IHC markers and to relate Notch-1 staining patterns to response to Notch inhibitors.

1747 Amyotrophic Lateral Sclerosis (ALS) Admission Rates and Metals Detected in Private Drinking Water Wells in Texas

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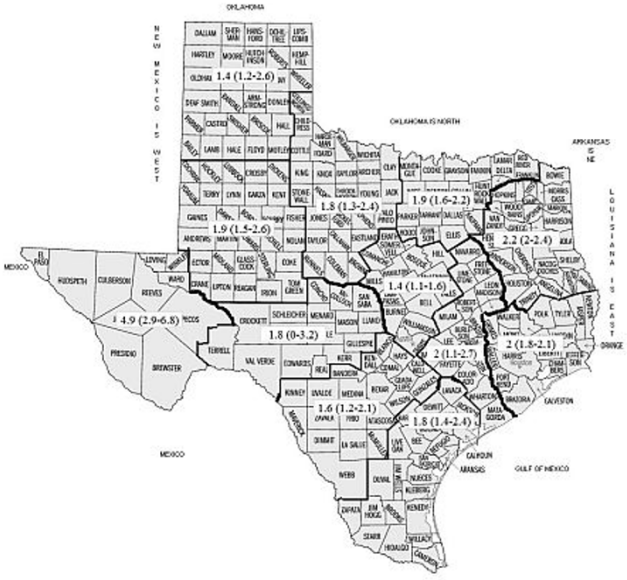
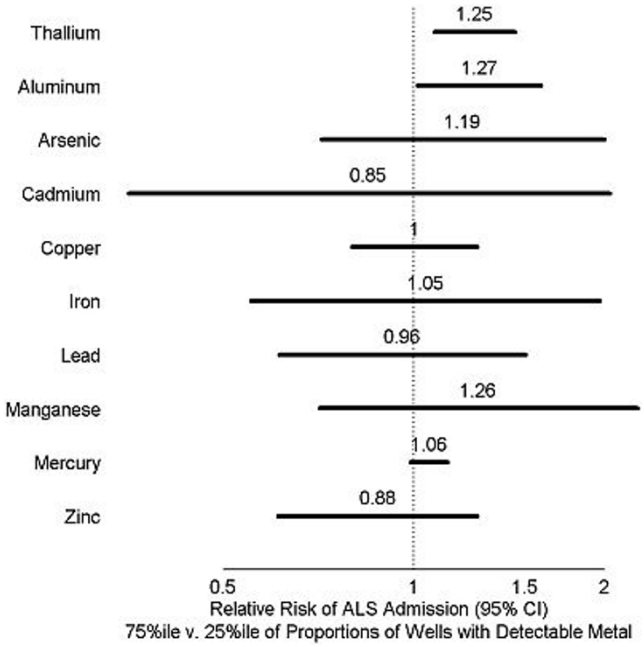
Background: The etiology of ALS remains obscure. Reports of geographic pockets of ALS suggest certain metal exposures may be a trigger in some cases. Texas (TX) has a combination of extensive agriculture and widespread use of private drinking water-wells; we hypothesized that evaluating ALS admissions by region and proportions of wells with detectable metals might produce evidence warranting further investigation of these contaminants.

Design: ALS admissions by quarter were obtained from the TX Hospital Discharge Inpatient Database; annual populations and proportions of populations older than 64 y, from the US Census; boundaries of TX regions and well water test results, from TX Ground Water Database. ALS admission rates were expressed by region as admissions per 100,000 person years for each of the quarters of 2004-2009. Number of wells tested positive metals was divided by total number of wells in each region.

Results:



Above are medians (interquartile ranges) of admission rates for the 12 regions. The highest median, 4.9, is nearly four-fold that of the lowest median, 1.4; the wide range raises the possibility that regional differences in exposure to metals via ground water might be of importance.



Log negative binomial regression produced the above results, adjusted for proportions of persons over 64 y, the year, and the quarter of the year. The roughly 25% increases in admission rates associated with increased proportions of wells with thallium (P=0.003) and aluminum (P=0.04) were not explicable by chance; a similar effect observed for manganese (P=0.05) might have been due to chance.

Conclusions: Proportions of wells with detectable thallium and aluminum are positively correlated with ALS admission rates, providing evidence these metals might play a role in ALS pathogenesis. The safety of thallium as an insecticide should be explored.

1748 Spectrum of Autopsy HIV Neuropathology in a Minority Population in the Post Anti-Retroviral Therapy (ART) Era

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Background: Primary HIV associated parenchymal brain pathology (HIV encephalitis, leucoencephalopathy and microglial nodule encephalitis) and secondary opportunistic infections have declined in the post ART era. We have investigated the spectrum of autopsy HIV neuropathology and incidence of Alzheimer type neurodegeneration in a predominantly racial and ethnic minority population with multiple comorbidities.

Design: We retrospectively studied neuropathologic findings in 20 HIV positive autopsy cases (2008-2012) which were classified into two groups (with or without ART therapy). The neuropathologic findings were categorized into (1) primary parenchymal HIV associated brain pathology (2) secondary pathology associated with immunosupression (3) non specific neuropathologic changes (4) no significant neuropathologic changes. Tau and beta-amyloid immunostain were performed on hippocampus and neocortical sections to evaluate Alzheimer type neuropathologic changes.

Results: The cohort consisted of 12 African Americans, 6 Hispanics and 2 Caucasians. 9 patients were on ART therapy. Primary HIV associated parenchymal brain pathology was present in 4 cases (25%) (1 case with both leucoencephalopathy and microglial nodule encephalitis). Secondary neuropathologic changes was present in 6 cases (30%). Seven brains (35%) showed variety of changes unrelated to direct HIV infection. No significant pathology was found in 2 brains (10%). Beta-amyloid deposition was absecent in all the brains while neurofibrillary tangles were identified in hippocampus of two patients (Braak stage II and III).

Table 1

Categories	Sub-categories	With ART	Without ART
Race/ethnicity			
	White	1	1
	Black	4	8
	Hispanic	4	2
Comorbidities			
	Hepatitis C	1	2
	Hepatitis B	2	1
Primary HIV associated neuropathology			
	HIV encephalitis	0	0
	HIV leukoencephalopathy	0	1
	Microglial nodular encephalitis	1	3
Secondary neuropathology associated with immunosupression			
	Cryptococcus meningoencephaliltis	0	4
	Aspergillous meningoencephalitis	1	0
	Progressive multifocal encephalopathy	0	1
Non-specific neuropathology		4	3
No significant neuropathology		1	1
Alzheimer type neurodegenerative changes			
	Beta-amyloid deposition	0	0
	Neurofibrillary tangles	1	1

Conclusions: Racial and ethnic minority population with HIV infection continue to have a high proportion of untreated cases, with high prevalence of both primary parenchymal HIV associated neruopathology as well as secondary opportunistic infections. However we did not find classical HIV encephalitis with multinucleate giant cells or Alzheimer type pneurodegenerative changes in our study.

Ophthalmic

1749 P16 and P53 Expression in Periocular Sebaceous Cell Carcinoma

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Background: Sebaceous carcinoma is a malignant neoplasm which often presents in the periocular region. In the United States, this lesion accounts for 1.3 to 4.7 % of malignant eyelid tumors. Histological diagnosis is often difficult, particularly in small biopsies in which tumor is often present only as scattered cells in the squamous or conjunctival epithelium. Determining the extent of such pagetoid spread can also be difficult in mapping biopsies or at margins of larger resections. The goal of this study was to evaluate p53 and p16 as potential immunohistochemical markers of sebaceous carcinoma, particularly intraepithelial tumor, in the ocular adnexa.

Design: Sebaceous carcinoma specimens were retrieved from the pathology archives of our institution, including 20 primary and 13 recurrent tumors. All tissues were fixed in 10% buffered formalin, routinely processed and paraffin embedded. Immunohistochemistry was performed using 5-µm sections and a Leica autostainer(Leica)for P16(Cintec)and a Ventana XT autostainer(Ventana Medical Systems)for P53(Ventana).

Results: We found 48% of the periocular sebaceous carcinoma cases to have intense nuclear p53 immunostaining. Additionally, we found 70% of sebaceous carcinoma of the periocular region to have intense p16 nuclear reactivity. 4 cases showed only strong p53 staining, while 9 cases showed only strong p16 staining. For both markers, immunoreactivity was relatively diffuse both within and between blocks. It was also roughly equivalent in both large subepithelial tumor nodules, and in the intraepithelial portion of the lesions. Together, our series revealed intense immunoreactivity to either p53 or p16 in 95% of cases, and weak or negative immunoreactivity in 5% of cases.

Conclusions: Major pathways implicated in the molecular mechanisms of skin cancer include the p53 and p16 pathways. While the expression of p53 has previously been examined as a potential marker of sebaceous carcinoma, p16 has not been well studied. Our findings confirm expression of p53 in a significant proportion(48%) of periocular sebaceous carcinoma. We found that an even greater proportion of tumors(70%) had intense p16 nuclear reactivity, suggesting that it could represent an additional marker with which to track tumor spread. Because some tumors expressed only p53 or p16, combined staining may represent the most effective way to highlight intraepithelial tumor, with 95% of cases showing immunoreactivity for one of the two markers.

1750 Stratifin as a Prognostic Marker in Ocular Surface Squamous Neoplasia

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Background: Ocular surface squamous neoplasia (OSSN) is the most common tumour of ocular surface with an incidence of 0.02 to 3.5 per 100,000. It encompasses spectrum of lesions ranging from dysplasia to squamous cell carcinoma (SCC). Stratifin (14-3-3σ)/HEM (human epithelial marker) which is an inhibitor of cell cycle progression, is a target of epigenetic deregulation in many carcinomas. However, its role in OSSN has not been investigated. In the present study, the association of stratifin expression with its promoter methylation status and their correlation with clinicopathological features in ocular surface squamous neoplasia patients was evaluated.

Design: Sixty four cases of histopathologically confirmed OSSN (44 SCC and 20 dysplasia) were included in this study. Each tumour was staged according to the AJCC TNM criteria. Immunohistochemistry and methylation specific PCR were used to evaluate expression of stratifin protein and its methylation status. Prognostic significance was assessed using Kaplan–Meier survival and Cox regression analysis.

Results: Loss of stratifin immunoexpression was observed in 75% cases (48/64) and promoter hypermethylation in 62.5% (40/64) cases of OSSN. Stratifin promoter hypermethylation was significantly associated with loss of its immunoexpression (38/40) (P=<0.0001). On correlation with clinical parameters, both loss of Stratifin immunoexpression and methylation were significantly associated with recurrence, tumor size ≥2cm (higher T category), orbital or intraocular invasion and reduced disease free survival (P≤0.05). Cox analysis showed stratifin to be an independent prognostic factor for OSSN (p =0.03).

Conclusions: Our results indicate that loss of Stratifin expression occours in OSSN and is caused by aberrant DNA methylation. Further, this loss of stratifin immunoexpression could prove to be a useful poor prognostic marker in OSSN patients after further validation.

1751 Ocular Infections, Diversity of Microorganisms and Clinical Associations

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Background: Infectious eye disease remains a significant cause of secondary blindness in the United States. Infectious keratitis alone is associated with a 35% risk of secondary blindness. Progression to endophthalmitis requiring enucleation is uncommon in the absence of comorbid conditions. This survey of patients with sight-threatening ophthalmic infections identifies the causative organisms and outcomes.

Design: Ophthalmic microbiology results were reviewed on patients with positive cultures from corneal and intraocular specimens over the period 2007-2012; 347 organisms were identified from 167 patients.

Results: The most commonly identified organisms in the studied population are listed in Table 1. The most common organisms were distributed over a range. In contact lens wearers, Pseudomonas aeruginosa (24%) was the most common isolated organism. In addition rare fungi, i.e. Aspergillus spp. (6 cases), Candida spp. (3 cases), and the protozoan, Acanthamoeba, were isolated (4 cases). 24 enucleations and eviscerations were identified, three of which had positive cultures for coagulase negative Staphylococcus, Corynebacterium and Pseudomonas aeruginosa. Predisposing factors included a history of trauma and corneal ulcers (45%), previous ophthalmic surgery (26%) and systemic diseases such as diabetes mellitus and sarcoidosis (20%).

Table 1. Positive ocular cultures

Organism	Prevalence
Coagulase negative Staphylococcus	34%
Methicillin sensitive Staphylococcus aureus	7%
Corynebacterium spp.	6%
Streptococcus, alpha-hemolytic	5.7%
Pseudomonas aeruginosa	5.5%
Haemophilus influenza	5.5%
Methicillin resistant Staphylococcus aureus	4.8%

Conclusions: The significance of CNS identification was not clear. CNS was regarded as a contaminant if recovered as a part of a group of organisms. CNS, MSSA, Corynebacterium spp. and alpha-hemolytic Streptococcus were considered commensal organisms and were clinically treated only if they were the sole organism recovered from the culture of a corneal ulcer. The mechanism of acquisition of MRSA in this location is not clear but MRSA organisms were most commonly resistant to Erythromycin and Clindamycin. A history of contact lens usage was confirmed in majority of the Candida (3/3) and Acanthamoeba infections (3/4). Progression to endophthalmitis was more commonly seen in patients with a history of trauma, ophthalmic surgery and systemic diseases.

1752 Glioblastoma of the Optic Nerve

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Background: Gliomas of the optic nerve are uncommon neoplasms, comprising approximately 3% of all gliomas, and 2% of all orbital tumors. Most optic nerve gliomas are pilocytic astrocytoma (WHO Grade I). Glioblastomas (GBM) (WHO grade IV) of the optic nerve and chiasm are rare, aggressive tumors that typically present with visual symptoms.

Design: We reviewed two cases of GBM arising in the optic nerve. Both patients were adult females who presented with visual complaints.

Results: Patient A was a 67-year-old female who presented with headaches, total vision loss in her left eye, and partial vision loss in her right eye. She had no previous ophthalmologic history, and no significant medical history. Magnetic resonance images (MRI) showed enlargement of the optic nerves and chiasm. Biopsy of optic nerve and chiasm demonstrated GBM. Follow-up MRI showed tumor extension to the visual cortex in the occipital pole. She expired 5 months following the biopsy. Patient B was a 61-year-old female who presented with blurred vision in her right eye, without any associated pain, nausea, vomiting, or other symptomatology. She had no previous ophthalmologic history, and had medical history only of hypertension and dyslipidemia. MRI showed evidence of an enhancing lesion of the right optic nerve and optic pathway (Fig. 1). A biopsy of the right optic nerve was performed, demonstrating GBM (Fig. 2). Microscopic examination of biopsies from both patients showed a hypercellular population of malignant astrocytes, characterized by cytological pleomorphism, mitoses, microvascular changes, and pseudopalisading necrosis.

Figure 1

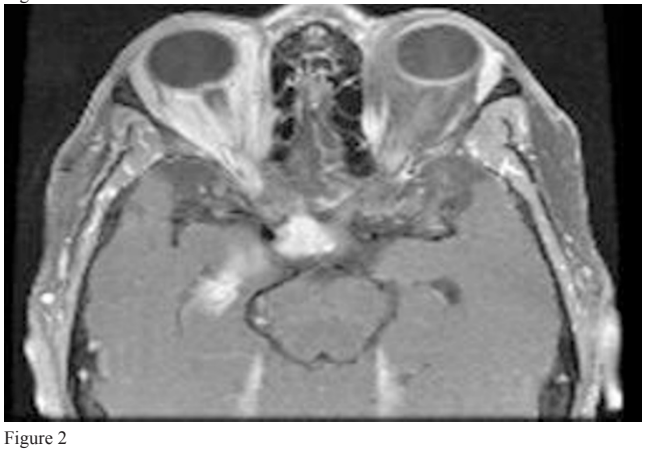

Figure 2