adenohypophysis. Finally, based on two index cases, we suggest that the category of pituictyomas should be expanded to include atypical spindle cell variants.

1503 Inflammatory Pseudotumors of the Central Nervous System

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Background: Inflammatory pseudotumor(IPT) is a disease with unsettled pathogenesis. The aim of this study is to investigate ALK-1 protein expression and IgG4-positive plasma cells(PC) in 3 intracranial IPTs.

Design: Three intracranial IPTs and the corresponding clinical information were retrieved from hospital archive.

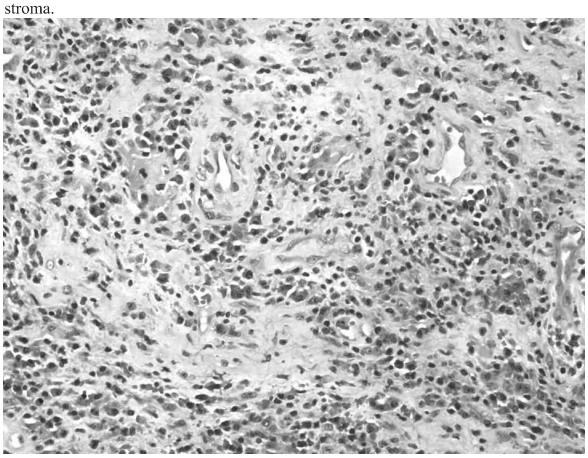
table 1

Location	Operation	No. of IgG4+ve PC/HPF(40x)
Cerebral falx & tentorium	Resection & radiotherapy	17
Right lateral ventricle	Resection	46
Right frontal region	Resection	41

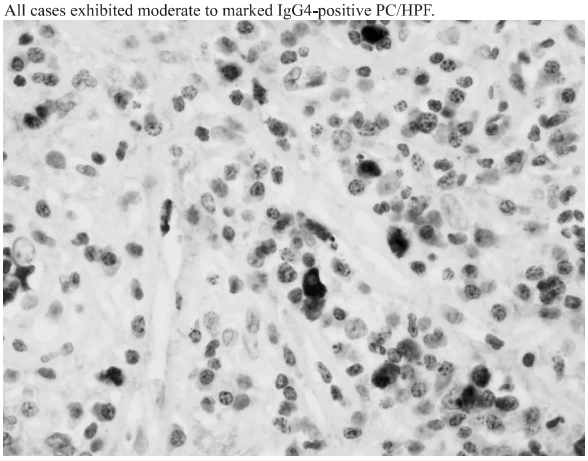
Clinical information and IgG4-positive plasma cell density in 3 patients.

Sections were examined under HE and immunohistochemical stainings including ALK-1 and IgG4.

Results: All cases displayed typical histologic features of IPT with dense lymphoplasmacytic infiltrate admixed with bland spindle cells in a collagenous stroma.



All cases exhibited moderate to marked IgG4-positive PC/HPF.



ALK-1 was negative.

Conclusions: ALK expression was absent in all cases and none of them recur. The detection of significant number of IgG4-positive PC in IPTs suggests that a considerable proportion of intracranial IPT may belong to the IgG4-related subgroup. Hence a trial of corticosteroid may be valid to avoid unnecessary risk taking neurosurgical procedures or in cases with incomplete tumor removal.

1504 Repeat Molecular Testing in Gliomas: A Retrospective Study of 53 Patients

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Background: Molecular testing for deletions on chromosomes 1p and 19q and for EGFR amplification has implications for the clinical management of certain glial tumors. The value of repeat testing in patients with multiple resections is unclear. The purpose of this study is to add to previously reported data assessing for evidence of molecular changes in gliomas which have undergone repeat testing.

Design: 53 patients (31 males; age mean 45.4 years) who had repeat molecular testing on specimens from two different resections for chromosome 1p deletion, chromosome 19q deletion and/or EGFR amplification by fluorescent in situ hybridization (FISH) were studied.

Results: Original diagnoses included 27 diffuse fibrillary astrocytomas (11 low grade, 3 anaplastic and 13 GBM), 16 oligodendrogliomas (11 low grade and 5 anaplastic), 6 mixed gliomas (4 low grade and 2 anaplastic) and 4 gliomas not otherwise specified. Nine tumors upgraded during the interval between the initial and the subsequent resection (4 astrocytomas, 2 oligodendrogliomas and 3 mixed gliomas).Paired results for 1p evaluation demonstrated a change in the profile from intact to loss in 1/50 patients (2%); the tumor upgraded from a low grade to anaplastic mixed glioma on the subsequent resection. Paired results for 19q evaluation demonstrated a change in profile in 4 of 41 patients (9.7%). Two of these tumors diagnosed as GBM on the initial and subsequent resections changed profile from 19q loss to intact. The remaining 2 tumors (1 astrocytoma and 1 mixed glioma) were initially 19q intact and changed to loss on the subsequent resection. The mixed glioma upgraded to anaplastic mixed glioma on the subsequent resection. There was no change in the EGFR expression in any of the patients tested (N= 34; 28 with no amplification, 6 with amplification). There was no change in the clinical management based on the repeated molecular tests in patients with discrepant repeat results.

Conclusions: There was only rare evidence of profile change in 1p and 19 q status (5/53 tumors) and no change in the EGFR amplification status with repeated testing. None of the tumors with change in molecular status were oligodendrogliomas. There appears to be no indication for repeat 1p/19q or EGFR FISH testing in gliomas at the time of repeat biopsy or resection.

1505 Isolation & Characterization of Brain Tumor Stem Cells (BTSC) in Human Glioblastomas (GBs)

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Background: Recent studies are suggesting that gliomas, develop from a subset of cells with self-renewal capacity stem-like cells. GB research, is showing evidences that brain tumor stem-cells (BTSC) drive tumorigenesis. BTSC isolated from GBs transplanted into immunodeficient animals generate GBs. However transplanted GBs cell lines devoid of BTSC do not generate tumors. BTSC are identified by their capacity to form neurospheres in culture, that express progenitor/ stem cell markers, like CD133, Nestin, Wnt, CXCR4, etc. Furthermore, BTSC expressing CD133 have been shown to be more resistant to radiation, being responsible of radiation treatment failure. Most studies were done in vitro or in animal models. We have addressed whether a population of BTSC exists in human GBs, that can be characterized phenotypically, to study patterns of expresssion & get insights into the biology of GBs.

Design: GBs disaggregated to single cells, were cultured with EGF & hFGF. Neuroespheres were harvested at 6 weeks. After centrifugation, the pellet was fixed, paraffin embedded and sectioned. Neuroespheres & original GB specimens from which they were generated, were immunostained with CD133, Nestin, Wnt1, CXCR4 & VEGFR3.

Results: CD133, Nestin, Wnt1, CXCR4 & VEGFR3 were expressed by neuroespheres with variable intensity, consistent with their heterogeneous nature. GBs displayed expression of these antigens by groups of neoplastic cells identified as BTSC with the following patters: -Frequent expression by perivascular cells, neoplastic vessels & perinecrotic palisades. -Increased expression by infiltrating marginal cells, versus the central tumoral areas. -High levels at the most anaplastic areas.

Conclusions: The patterns of expression of the BTSC subpopulation in GBs argues for their role as cancer driving cells. 1) The expression of stem/progenitor markers support their property as self-renewal neoplastic elements. 2) The perivascular and endothelial proliferating cells location of BTSC, argues for a role in neoplastic angiogenesis, a hallmark of glioma anaplasia. 3) The high levels of BTSC observed at infiltrating margins and perinecrotic palisades, are in keep with their suggested invasive function. This raises the importance of using BTSC as therapeutic targets to improve treatment success.

1506 Molecular Alterations of PDGFA and PDGFRA in Gliomas

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Background: Malignant gliomas are the most prevalent primary brain tumours, have an aggressive clinical course and lack effective treatment options. PDGF signalling is one of the key regulators of glioma development. The efficacy of anti-PDGFRA drugs for the management of patients with glioblastomas is currently being tested in clinical trials. The aims of this study were to determine the expression of PDGFRA and PDGFA and the underlying genetic mechanisms driving their expression in a large series of gliomas.

Design: We investigated the frequency of PDGFA and PDGFRA expression by immunohistochemistry in 169 gliomas and screened for *PDGFRA* gene mutations and gene amplification in 86 and 57 gliomas using a combination of direct sequencing, quantitative copy number PCR and microarray-based comparative genomic hybridisation.

Results: We found that PDGFA was largely expressed in different glioma histological types and its absence was associated with a poor prognosis. PDGFRA was significantly expressed at high levels in malignant astrocytic tumours. Moreover, we have observed the existence of putative PDGFA/PDGFRA autrocrine/paracrine loops in glioblastomas. Finally, although *PDGFRA* gene activating mutations were not found, *PDGFRA* gene

amplification was observed in 21% of gliomas and was significantly associated with PDGFRA overexpression in diffuse astrocytomas.
Conclusions: The present study describes a comprehensive molecular analysis of PDGFA and PDGFRA in gliomas. Taken together, these results provide a molecular basis for anti-PDGFRA therapies in gliomas.

1507 Quantitation of Large Subsarcolemmal Mitochondrial Aggregates Improves Specificity for Diagnosis of Mitochondriopathy in Children

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Background: In the diagnosis of mitochondriopathy the presence of ragged red fibers and COX-negative fibers is helpful, but these features are uncommon in muscle biopsies from children. Until recently >2% of myofibers containing subsarcolemmal mitochondrial aggregates (SSMA) was proposed as a minor criterion for diagnosis of mitochondriopathy. The current authors suggested previously that only large SSMA (LSSMA), ≥4μm in thickness, are useful for the diagnosis of mitochondriopathy. The current study compares the sensitivity and specificity of % of myofibers containing LSSMA, SSMA, type 1 myofiber, and for each patient, the lowest individual electron transport chain (ETC) complex activity in the diagnosis of mitochondriopathy.
Design: Only patients with previously identified LSSMA and ETC testing in muscle were included in this study. The discriminative performances of LSSMA(%), SSMA(%), type I myofiber predominance(%), and lowest individual ETC complex activity (% of mean control) result were evaluated for the diagnosis of mitochondriopathy using receiver operating characteristic (ROC) analysis. Results are expressed as mean±SD.
Results: In 35 patients with LSSMA, 9 [age 7.3±7.8y] had mitochondriopathy (group 1) and 26 [age 4.3±2.9y] had no evidence of mitochondriopathy (group 2). Group 1 patients had increased LSSMA (p=0.007) compared to group 2, 4.7±3.4% vs. 1.7±1.0%, respectively. Type I myofiber (%) and SSMA (%) were similar between groups. ETC complex activities were similar except for decreased complex I+III activity in group 1 (p=0.008). ROC analysis results are summarized in the table. Logistic regression modeling indicated that the diagnostic performance was significantly improved (Area Under the ROC Curve=0.938) with the combined use of LSSMA and ETC testing

Comparison of ROC Results

	AURC	Cutoff	P-value	Sensitivity	Specificity
Lowest ETC activity (%)	0.80	≤40.0	0.0001	77.8	88.5
Large SSMA (%)	0.81	>3.3	0.0013	66.7	96.2
Type I Myofiber (%)	0.59	>60.0	0.44	55.6	68.0
SSMA (%)	0.54	>28.3	0.71	22.2	100.0

AURC; area under ROC curve **Conclusions:** Because of improved specificity, a LSSMA >3.3% should be considered as a potential major criterion for diagnosis of mitochondriopathy in children.

1508 Caveolin-1 Expression Predicts Outcome in Oligodendroglial Tumours Regardless of 1p/19q Status

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Background: Caveolin-1 (Cav-1) is the basic component of caveole, omega-shaped membrane microdomains involved in various cell functions. In tumours, Cav-1 can be either overexpressed, suggesting a pro-neoplastic role, or downregulated: therefore, its role in oncogenesis is still debated. Regarding brain tumours, our group demonstrated that Cav-1 is significantly more expressed in astrocytic-derived tumours than in oligodendrogliomas, suggesting how this marker could be used as a valuable tool in the differential diagnosis between these two categories. Moreover, in tumours of astrocytic origin, we reported that Cav-1 expression increases accordingly to tumour grade, thus suggesting a tumour-aggressiveness related phenotype and envisaging a possible role for Cav-1 in predicting patients' prognosis.
Design: We here studied Cav-1 expression in oligodendroglial tumours, such as oligodendrogliomas (OD), oligoastrocyromas (OA) and glioblastomas with oligodendroglial component (GBMO) to evaluate its potential role as a prognostic factor and to determine if its expression is related to 1p/19 deletion, to date the hallmark prognostic factor for these gliomas. Eighty-seven cases of ODs, OAs and GBMOs were collected, and studied for 1p/19q status and Cav-1 expression by FISH analysis and immunohistochemistry respectively.
Results: Cav-1 was expressed in a minority of cases (21.8%), mostly grade III OAs and GBMO; 1p/19q deletion was expressed in 45,97% cases, mostly grade II and III ODs. The correlation between 1p/19q deletion and loss of Cav-1 staining was proven to be statistically significative (p= 0.0002), as well as a single chromosome deletion (1p or 19q), defining a group of patients with better prognosis. Moreover, Cav-1 positivity independently recognized a subset of tumours with worse prognosis (Mantel-Cox=0.03), even if concurrently carrying 1p and/or 19q deletion.
Conclusions: We here provide the first evidence that Cav-1 is a new trustworthy, easy to manage, independent prognostic marker in oligodendroglial-derived tumours regardless of the 1p/19q status Since Cav-1 has been also associated with mechanisms underlying multi-drug resistance, we feel thus entitled to preliminarily suggest that the worse outcome in Caveolin-1 positive patients in our series could be at least partially related to an acquired chemotherapy resistance.

1509 Clinicopathological Study of Extraventricular Neurocytomas

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Background: From 1992, parenchymal counterpart of central neurocytoma (CN), extraventricular neurocytoma (EVN) started to be recognized, which share the histopathogical features of the CN but are known to show a wide morphological spectrum.
Design: Five recent cases of EVNs along with the clinicopathological and radiological findings are reviewed.
Results: The mean age of the patients was 36.2 years old (6 yrs~66 yrs) and a female predominance (M:F=1:4) was found. The most common symptom was seizure (n=4) and the tumors were located in the temporal lobe (n=3), frontal lobe (n=1), and hippocampus (n=1). MRI showed nonenhancing cystic lesion (n=2), infiltrating solid mass (n=2), and well circumscribed mass with focal high signal intensity lesion on T2 and FLARE (n=1). Near total resection of the tumors were performed in every case. The tumor cells in all cases, regardless of the tumor grade, were composed of small round cells with round nuclei and clear or eosinophilic cytoplasm. These cells were arranged in sheet, in association with broad zone of fine neuropils. They superficially mimicked oligodendroglioma, but fried egg appearing cells were only focally observed. The cellularity was variable area by area. Often smaller ganglioid cells with nuclei that are larger and paler than neurocytes were detected. Three high grade ones showed high mitotic activity (7 to 9/10 HPF) and high level of MIB-1 labeling Indices (6 ~29 %). Two of them had vascular endothelial hyperplasia and necrosis. Almost tumor cells were immuno-labelled for synaptophysin and NeuN, and, additionally, expressed the nestin. GFAP expressing cells were observed focally, but pseudopapillary configuration was not shown. Ultrastructurally, neural tubules and synapses with synaptic junctions and synaptic vesicles were well observed. 1p/19q FISH study perfomed in 2 cases revealed no deletions. Radiotheraphy was offered to three patients with high grade ones. There were no case of recurrence in the course of follow-up periods (3 ~26 months) even though the follow up duration was not sufficiently long enough to confirm the biologic behavior.
Conclusions: EVNs were occurred in the patients with broad age ranges and epilepsy was most common symptom. Without immunohistochemistry, EVNs had a diagnostic pitfall due to spectrum of tumor cell morphology and similarity to oligodendrogliomas. More reports about its clinicopathological, biological and genetic studies are needed to understand and to have confidence upon this tumor.

1510 Assessment of the 1p/19q Deletions at Different Areas in Biphasic Oligoastrocytomas by Using Chromogenic In Situ Hybridization

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Background: Oligoastrocytomas (OAs) are mixed gliomas composed of tumor cells morphologically resembling oligodendroglioma and diffuse astrocytoma. Albeit the status of 1p/19q deletions in oligodendrogliomas is well-known, isolated or combined losses of 1p/19q in OA remains to be elucidated. The goal of this study was to evaluate the 1p/19q deletions by using CISH at different tumor areas in a series of bona fide "biphasic" OAs of different grades of malignancy.
Design: CISH was performed on formalin-fixed paraffin-embedded cores in different tumor areas of 12 OA, intermingled ("diffuse") variant (4 grade II, and 8 grade III) by using a TMA block . The patient's mean age was 40 years (11-54 years) with 2:1 male/female ratio. The presence or absence of chromosome locus 1p36 and 19q13 was analized in different tumor areas [oligo *vs* astrocytic areas]. The cut-off values was established by counting 500 nuclei in normal brain tissue from patients with intractable epilepsy. It was analyzed a minimum of 200 tumor nuclei for each set of probes without the knowledge of the diagnosis.
Results: Were have found combined/isolated losses of 1p/19q in 50% of the tumor samples.

Table 1. Status of 1p/19q deletions in Oligoastrocytomas according different grades of malignancy.

Grade	1p/19q	1p	19q	No deletions	Total
II	1	1	—	2	4
III	1	2	1	4	8

The combined 1p/19q losses were detected in 2/12 cases and were present in both astrocytic and oligodendroglial components. The isolated loss of 1p was detected in 3/12 cases (25.0%). Interestingly, the 1p loss was present in both components in one grade III OA. The remainder exhibited isolated 1p loss in astrocytic but not in the oligodendroglial area (grade II) and vice-versa (grade III OA). The isolated loss of 19q was found in both components and it was present in one case.
Conclusions: 1p/19q deletions are not an uncommon event in OAs. Interestingly, in these cases, regardless if they have combined or isolated losses, the chromosomical deletions were found in both oligo and astrocytic components in 4/6 cases, which could reflect the clonal origin for both components. Furthermore, CISH is a low-cost technique, easy to perform and has a beneficial tool in the diagnosis assessment of 1p/19q status in gliomas.

1511 Adhesion Molecule Expression in Primary, Recurrent, and Metastatic Medulloblastomas

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Background: Medulloblastoma spreads by leptomeningeal dissemination rather than the infiltration that characterizes other CNS tumors. Adhesion of tumor cells to the meninges is necessary for this spread and may contribute to the survival and proliferation ofthe tumor implants. The mechanisms accounting for this are not known.
Design: This study represents an immunohistochemical study of molecules which may govern medulloblastoma adhesion to leptomeninges. Search of the UHN surgical archives uncovered 57 adult medulloblastomas from 42 patients. In addition to primary resections for all patients, there were 13 recurrences in the posterior fossa and 2 instances of leptomeningeal dissemination. Immunohistochemistry was performed with antibodies to transmembrane adhesion molecules: Beta1 Integrin, NCAM, L1CAM, NCadherin and extracellular matrix molecules: Collagens I and IV, Tenascin, Fibronectin, Vitronectin, Trombospondin and Laminin.
Results: Evaluation of the stained sections showed increased Beta1 Integrin reactivity in recurrent and leptomeningeal tumors compared to their matched primary resections.