O-12-178 The biological behaviour of the pilocytic astrocytoma by Ki-67-and p53-immunostaining related to neuro-imaging

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Introduction: One-third of patients surgically treated for a cerebellar pilocytic astrocytoma have postoperative residual tumor. Tumor remnants may remain "silent", regress or show rapid progression. Attempting to predict the biological behaviour of the tumor remnant we studied tumor tissue with markers for the Ki-67 protein, known to be elevated in proliferating cells, and the p53 protein, which is upregulated in case of a p53 gene mutation.

Methods: 39 patients operated for a pilocytic astrocytoma; in the cerebellum (28), optic tract and hypothalamic region (6), 3rd ventricle (1), spinal cord (1) and supratentorial hemisphere (3), were retrospectively analysed regarding neuroradiological follow-up. 4 patients were operated twice, in total 43 tumor specimens were stained with the two markers for Ki-67 (the MIB-1 marker) and p53. Results were related to the tumor behaviour as determined by follow-up CT- and or MRI-scans.

Results: From the 39 patients 19 showed postoperative residual tumor. Ten of these progressed during follow-up ranging from 2 to 56 months (mo) (mean 12.8 mo). From the other 9 tumor remnants 7 remained stable and 2 regressed during follow-up from 12 to 59 mo (mean 29 mo). The Ki-67 labelings index (LI) in the 43 samples ranged from 0 to 19% with a mean of 3.9%. Progressing tumors had a mean Ki-67 LI of 5.8%, non-progressing of 2.6%. Among all Ki-67 negative tumors (n = 19) were 6 residual tumors from which 2 showed progression. Among the Ki-67 positive tumors (n = 24) there were 13 residual tumors, from which 8 showed progression (difference not significant; p = 0.08, Fisher exact test). Four reoperated patients all showed lower Ki-67 LI values in their second tumor sample p53 LI's ranged from 0 to more than 50%. The two groups with and without tumor progression had the same mean scores for p53 LI. There was no difference in number of tumor-progressions in the group with low p53 LI's, compared to the group with high p53 LI's. Subsequent tumor samples of re-operated patients either had higher or lower p53 LI values.

Conclusion: Ki-67 LI negative tumors show a strong tendency towards a more benign behaviour than the positive tumors. Ki-67 LI negative tumors are unlikely to show progression. Partial debulking of a pilocytic astrocytoma may decrease the proliferative potential of such a tumor possibly by decreasing the vascular feeding of the tumor remnant, as is reflected in the lower Ki-67 LI of the tumor samples of the re-operated patient. Previous work with BudR labeling supports these results. P53 labeling has no role in the determination of the biological behaviour of this tumor, this is in concordance with the only 1 reported case of a proven p53 mutation among more than 50 of those tumors. The important role of the p53 suppressor gene in tumorigenesis of high grade astrocytomas seems to be lacking in the pilocytic astrocytoma. Patients with a pilocytic astrocytoma tumor remnant having a positive Ki-67 LI should be closely followed by frequent CT- or, preferably MRI-scans. Progression of this tumor without neurological signs may be an indication for re-operation or additional therapy.

O-12-179 Clinicopathological study of diffuse type brain stem gliomas: Analysis of 40 autopsy cases

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Introduction: There are few reports on cell kinetics of brain stem gliomas. The authors therefore examined 40 autopsy cases of diffuse type brain stem gliomas for histological typing, proliferative potentials, tumor extension and prognosis.

Methods: The histology was classified according to the WHO classification. Proliferative potentials were immunohistochemically determined with an anti-Ki67 protein monoclonal antibody (MoAb)(MIB1) and an anti-PCNA MoAb (PC10). Parencymal and leptomeningeal spread was examined microscopically.

Results: Fourty patients (21 male, 19 female; mean age 11.9 y.o.) comprised 34 glioblastoma (GM), 5 anaplastic astrocytoma (AA) and 1 astrocytoma (A). In 16 GMs, the tumors grew within the brain stem with (N = 4, type II) or without (N = 12, type I) leptomeningeal dissemination; in the remaining 18 GMs, the gliomas spread beyond the brain stem with (N = 8, type IV) or without (N = 10, type III) subarachnoid seedings. In 5 AAs, 4 were type I and 1 type II. One astrocytoma showed type I growth. The MIB1 immunohistochemistry and PCNA staining were evaluable in 66% (25/38) and 87% (33/38), respectively.

In GMs, MIB1 proliferating cell indices (PCIs) ranged 8.0–45.4% (mean 20.4%) and PCNA PICs ranged 14.7–83.0% (mean 37.0%). In AAs and one astrocytoma, mean PCNA PCIs was 12.7% and MIB1 PCIs, evaluable only in one cases, was 2.9%. Median survival was 32 weeks for GMs, 54 weeks for AAs and 56 weeks for one astrocytoma.

Discussion and Conclusions: These data suggest that the majority of diffuse type brain stem gliomas are GM and a few AA or A, the latters of which less infiltrative and proliferative and thus have a little better prognosis than the former.

O-12-180 Chromosomal deletions rather than microsatellite instability are important in the pathogenesis of oligodendrogliomas

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Introduction: Molecular analysis of loss of heterozygosity (LOH) as a method to identify regions of non-random losses of genetic material has successfully been used in cloning of numerous tumor suppressor genes. Microsatellite instability (MI) resulting from defective mismatch repair has been implicated as an independent pathogenetic mechanism in various neoplasms. The purpose of this study was to identify regions with high frequency of LOH and to assess the role of genomic instability in oligodendroglioma development.

Methods and Results: A set of 132 microsatellite markers covering chromosomes 1 through 12 and 15 through 21 was used to screen 25 oligodendrogliomas for MI and for LOH. DNA was isolated from blood and tumor samples obtained at surgery and PCR-amplified using microsatellite marker primers. The amplified DNA fragments were electrophoretically resolved and patterns of corresponding blood and tumor compared. Loss of one tumor band in a constitutionally heterozygous patient was diagnosed as LOH whereas an addition or shift of tumor alleles as MI. High frequency LOH regions (>30%) were identified on chromosomes 1, 4, 6, 11, 17 and 19. Three loci on chromosome 1 and two on chromosome 17 exhibited significantly higher LOH frequency in anaplastic than low-grade oligodendrogliomas ($p > 0.05$). Only 44/2481 (1.8%) loci exhibited MI.

Discussion: The low frequency of MI allows us to conclude that defective mismatch repair is not important for oligodendroglioma development. However, multiple regions of high LOH frequency indicate presence of putative tumor suppressor genes. In addition, two regions were found more frequently deleted in anaplastic than low-grade oligodendrogliomas suggesting presence of genes important for oligodendroglioma progression. We are currently investigating these regions for candidate oligodendroglioma genes.

Tuesday, 8 July 1997 **14:00-16:30**

O-13 Cerebrovascular Disorders – Aneurysms: Surgical and Endovascular Management

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O-13-181 Transsylvian approach for the anterior communicating artery aneurysm

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Although we usually operate on the patient with an anterior communicating artery (A-com-a) aneurysm by the pterional approach, nowadays we are trying a transsylvian approach. We would like to report the advantages in this methode.

Since January 1990, we performed this approach in 55 cases. After a routine right fronto-temporal craniotomy, the arachnoid from Sylvian fissure to the prechiasma is opened widely and the frontal lobe is retracted en masse. After recognizing the right A_1, the contra-lateral A_1 is easily confirmed usually between right A1 and optic nerve or chiasma through the transsylvian route. Recognizing both A_1 makes the manipulation around the aneurysm easier and faster. About 1.5 cm of arachnoid in anterior interhemispheric fissure is dissected sharply and the right A_2, the neck of the aneurysm and the opposite A_2 are recognized respectively.

Only one case (1.8%), which was a quite high position A-com-A, experienced the complication of a slipping clip because the gyrus rectus displaced the head of the clip after operation. The merit of this technique is as follows: (1) In almost all cases of A-com-A aneurysms even when the right A_1 is hypoplastic, we can perform a right craniotomy. (2) We minimize the retraction of frontal lobe. (3) There is no need of sucking the gyrus rectus even in high positioned aneurysm.