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LETTER TO THE EDITOR

Age at diagnosis and loss of heterozygosity on chromosome 1p and 19q in oligodendroglial tumors

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Abstract The age distribution and incidence of loss of heterozygosity (LOH) of 1p and 19q was analyzed in 85 oligodendroglial tumors WHO II and III. The peak of tumor manifestation was in the age group of 35 to 55 years. There was no association between age at diagnosis and LOH incidence. We conclude that the prognostic effect of age on survival is not mediated by LOH 1p/19q.

Keywords Oligodendroglioma · Oligoastrocytoma · Loss of heterozygosity · LOH 1p/19q · Age at diagnosis

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Dear Editor,

Age is a strong predictive factor of survival in patients with brain tumors. As a pre-treatment variable in low-grade gliomas the effect of age on survival is more prominent than the effect of radiotherapy [1, 2]. In addition, age at the time of initial tumor diagnosis is inversely correlated to the time of malignant progression from low grade to anaplastic astrocytoma [3]. Theoretically, age could affect one or several of the genetic events, which facilitate tumor initiation and progression. Distinct age-related genetic alterations were identified on chromosome 7 in anaplastic astrocytoma, which defined subsets of patients with respect to survival [4]. In glioblastoma TP53 mutation as well as loss of heterozygosity (LOH) on chromosome 1p were age-dependent and correlated with survival [5]. Our study aimed to investigate the age distribution of LOH 1p and 19q in low-grade and anaplastic (WHO II and III) oligodendrogliomas (OD) and oligoastrocytomas (OA). In anaplastic oligodendroglial tumors LOH on 1p and 19q correlates with survival and sensitivity to chemotherapy [6, 7].

Patients were divided into four groups according to histology and WHO grade. Patient groups were subdivided into 'young' and 'old' according to the median age of each group. The association between age and occurrence of LOH was then assessed using SPSS software (version 10.0.7) applying the χ^2-test.

LOH of 1p/19q was determined by polymerase chain reaction (PCR) of the microsatellite polymorphisms D1S508, D1S2734, D1S199, D19S219, D19S112, D19S596, and D19S412. Amplification was performed from tumor DNA extracted from formalin-fixed paraffin-embedded tissues and from normal reference DNA extracted from the patient's EDTA peripheral blood.

Size and relative amounts of the alleles were determined by electrophoresis on an ABI Prism (310 capillary sequencing automate [8]). Alternatively, PCR was performed from the microsatellite markers D1S468, D1S1612, D1S228, D1S214, D19S219, D19S412 and D19-HRC and analyzed either with sequencing gels, or using an ABI Prism (3100-Avant and the GeneMapper software 3.0). LOH was determined by measuring the peak area from each of the alleles produced from the tumor and corresponding normal DNA, respectively. Diagnostic criteria for LOH required the calculated ratio of the peak areas to be less than 0.5 [9].

Macroscopically complete resection was achieved in 76% of patients. About 8% underwent partial resection, and in 16% of the cases, surgery was performed with the intention to obtain a biopsy. The median age at the time of tumor diagnosis was 46.0 years (mean 46.1 ± 12.1 years (SD)) for all 85 patients. Our series included 17 OD II (median age, 43.0, range: 27–62 years), 9 OD III (45.0, 37–66), 34 OA II (49.0, 16–75), and 25 OA WHO III (46.0, 25–70). About 46% were females. Figure 1a presents the age distribution of OD and OA. Combined LOH 1p/19q was found in 76 and 89% of OD WHO II and OD WHO III, respectively. For OA these numbers were 59% and 44%, respectively. Isolated LOH 1p was found in one patient each with OD III, OA II and OA III. Isolated LOH 19q was found in one patient each with OD II and OA II, but in 7 of 25 (28%) of OA III. In our series, a trend for lower incidence of LOH 1p/19q was found in patients older than 55 years (Fig. 1b). However, this trend did not reach statistical significance ($\chi^2 = 2.545$, $P = 0.280$).

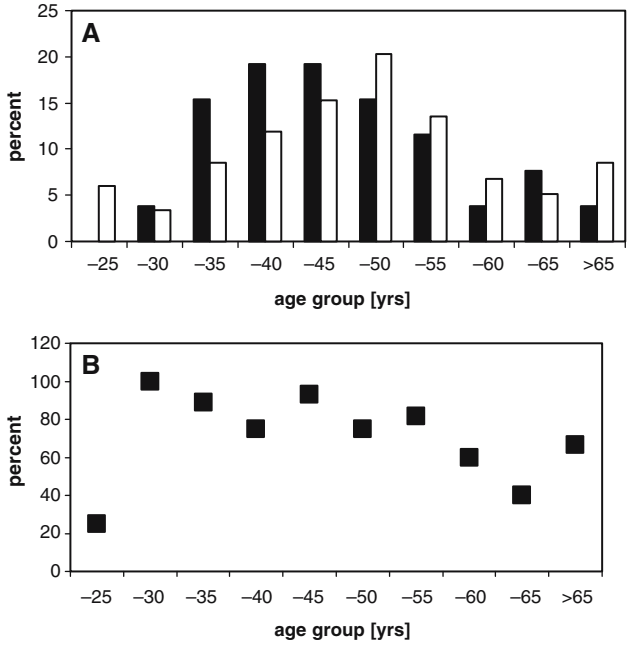

Fig. 1 (**a**) Age distribution of all patients and percentage of OD (oligodendroglioma, white bars) and OA (oligoastrocytoma, black bars). The highest incidence of the disease is in the age group from 35 to 55. (**b**) Incidence of LOH in different age groups. The data from OD and AO are pooled

Our data confirm earlier reports, which demonstrate that LOH occurs more frequently in oligodendroglial than in oligoastrocytic tumors [6]. The results shown in Fig. 1b suggest a moderate decrease in incidence of LOH 1p/19q with age. However, our statistical analysis did not disclose a significant association between the age at diagnosis and LOH incidence for the whole group of patients as well as for subgroups assembled according to WHO grade and histology.

LOH 1p/19q is considered an 'early event' during the accumulation of genetic changes resulting in the development of oligodendroglial tumors [10, 11]. Because somatic genetic alterations accumulate during life, the well-known effect of age at diagnosis on the prognosis of glioma patients might be an unspecific effect of a number of thus far uncharacterized mutations. In various other neoplasms outside the brain, such as myelomas, mutations have been found to occur with a specific age distribution, indicating a particular biological vulnerability in defined periods of life [12].

In oligodendroglial tumors inactivation of the methylguanine-DNA methyltransferase (MGMT) gene by promoter methylation was more frequent in patients older than 40 years. In the same population, no age effect on LOH 1p/19q distribution was observed [13]. These results are surprising, because, even though older age is an indicator of poor prognosis, the molecular parameter of MGMT promoter hypermethylation might have opposite effects, because it confers sensitivity to DNA-damaging chemotherapy in malignant gliomas [14].

In summary, our data suggest that the impact of age is not mediated by LOH 1p/19q. At the present time, it remains unknown how age influences survival. Other hitherto unknown genetic events may account for the effect of age on prognosis. Methods such as microarray comparative genomic hybridization (CGH) or multiplex ligation polymerization analysis (MLPA) will allow the detection of more subtle molecular changes in the deleted genomic regions. At the same time, they will result in a more detailed understanding of the genetic changes in these tumors.

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