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Original research article

The correlation of clinical and chromosomal alterations of benign meningiomas and their recurrences

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ABSTRACT

Meningiomas (MGs) are the frequent benign intracranial tumors. Their complete removal does not always guarantee relapse-free survival. Recurrence-associated chromosomal anomalies in MGs haves been proposed as prognostic factors in addition to the World Health Organisation (WHO) grading, tumor size and resection rate. The aim of this study was to evaluate the frequency of deletions on chromosomes in sporadic MGs and to correlate them with the clinical findings and tumor behaviour. Along with survival, the tumor recurrence was the main endpoint. Chromosomal loss of heterozygosity (LOH) was studied. 46 benign MGs were subjected to the analysis, complete tumor resection was intended and no early mortalities were observed. Incomplete removal was related to parasagittal location and psammomatous hisptopathology ($p < 0.01$). Chromosomal alterations were present in 82.6% of cases; LOH at 22q (67.4%) and 1p (34.8%) were the most frequent and associated with male sex ($p = 0.04$). Molecular findings were not specific for any of the histopathologic grade. Tumor recurrence (14 of 46) correlated with tumor size (≥35 mm), LOH at 1p, 14q, coexistence of LOH at 1p/14q, 10q/14q, 'complex karyotype' status (≥2 LOHs excluding 22q), patient age (younger <35), and Simpson grading of resection rate (≥3 of worse prognosis). The last 3 variables were independent significant prognostic factors in multivariate analysis and of the same importance in recurrence prediction (Receiver Operating Characteristic curves comparison $p > 0.05$). Among the cases of recurrence, tumor progression was observed in 3 of 14. In 2 cases, LOH on 1p and/or coexistence of LOH 1p/14q correlated with anaplastic transformation.

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1. Introduction

According to the recent reports (2007–2011 USA registry), meningiomas (MGs) are the most frequently diagnosed brain tumor (36.1%), exceeding half of all intracranial benign tumors (53.7%) [1]. A MG is a frequent incidental finding in magnetic resonance imaging (MRI) of the head, but is revealed in only 2% of autopsies [2,3]. To date, the etiology of these tumors has not been sufficiently explored. Researchers attempted to use molecular biology to explain the recurrence phenomena of a completely removed MG. The criteria of the diagnosis of Grade 1–3 MG (respectively benign, atypical and malignant) were based on clinicopathological correlations made by the World Health Organisation (WHO) [4,5]. The 2007 revision of the WHO classification identified 14 heterogeneous histopathological subtypes [6]. According to WHO ~80% of all MGs are slowly growing Grade 1 tumors [7]. Whereas the Grade 2 or 3 are rarely diagnosed. Moreover, it has been suggested that 17–35% of Grade 2 and 54–70% of Grade 3 progress from benign subtypes [8,9]. The WHO grading of MGs remains controversial, nonetheless it has facilitated estimating patient management [10]. Parallel to the resection rate, the WHO classification is still regarded as the most potent prognosis-associated factor [10,11].

Almost 40% of the totally removed Grade 2 tumors relapse, comparing to only 5% of Grade 1 MGs [12]. However, the diagnosis of one of nine subtypes of benign MG (called Grade 1, non-cancerous) does not preclude its worse clinical behaviour in some patients [13]. Finally at least a quarter of patients harbouring a benign MG experience a tumor relapse within 20 years [14]. Therefore, some prognosis-related factors have been proposed to identify a clinically aggressive subset of benign MGs: familial occurrence, patient age, tumor location, Ki-67/MIB-1 labelling index, telomerase activity, proliferating cell nuclear antigen [15–17]. Recently the molecular biology has attempted to explain the recurrence phenomena of a completely removed MG [10,18–20].The milestone was the identification of the *NF2* gene on the long arm of chromosome 22 (22q12.2) that is responsible for the production of merlin (a cytoskeletal protein). Mutation or loss of *NF2* is associated with the multiple tumor occurrence and is found in up to 70% of sporadic MGs [21,22]. Since 22q was established the most frequent aberration in MGs, authors focused on cytogenetic profiling of MG tumorigenesis or progression. A broad array of the loci was postulated, including 1p, 3q, 6q, 9p, 9q, 10p, 10q, 14q, 14p, 18p, 18q and 22q [10,20,23,24]. Moreover, single nucleotide polymorphism (SNP) demonstrated loss of heterozygosity (LOH) on several loci within one cytoband in MGs [21]. Surprisingly, the investigators sparsely focused on the correlation of molecular findings with clinical data. Benign tumors with known genomic status were rarely followed-up, thus we still are not certain of the relapse-associated chromosomal aberrations [18,20,25–27]. In clinical perspective, the disease-free survival is actually the most crucial outcome measure. The estimation of relapse-specific genomic landscape of MGs is strongly desired [18]. A prognosis based on molecular and histopathological findings is believed to prompt a decision-making process tailored to each individual patient [20].

2. Materials and methods

2.1. Study design

The aim of the study was to correlate the recurrence status and time to relapse with chromosomal alterations in sporadic Grade 1 MGs. The analysis included clinical data such as age, sex, tumor location and rate of recurrence. Multivariate analysis was used to bring reliable *molecular* recurrence-related prognostic factors.

2.2. Patients

Tumor tissues were obtained from patients presenting with non *NF1*/*NF2*-related intracranial MG. All consenting patients were managed operatively at the Neurosurgery Department (coded for peer review process) from 1999 to 2007. Intent-to-treat patient selection was applied; complete resection was intended in all cases and the Simpson grading was used for assessing the extent of tumor removal [28]. The study group consisted of 46 patients with benign (WHO Grade 1) sporadic MGs. The demographics are presented in Table 1. Pre- and postoperative imaging was evaluated, but was not standardised throughout the study (either computer tomography or MRI was performed based on the accessibility). The details of the surgical techniques performed are beyond the scope of this article purpose. Baseline and postoperative neurological status was not evaluated. Postoperative radiotherapy was not offered. All patients were followed-up either by outpatient clinic visits, mail, e-mail or phone.

Table 1 – Patient characteristics, histopathological diagnoses and the extent of resection.

	n	% or ratio
Demographics		
Sex (female:male)	33:13	Ratio:2.54
Age [mean ± SD	51.1 ± 12.9	
median, min–max]	50 (20–80)	
Location		
Supra-/infratentorial	38:8	ratio:4.75
Convexity	25	54.3%
Parasagittal or falx	15	32.6%
Cranial base	21	45.7%
Sphenoid	13	28.3%
Pyramid	5	10.9%
Size (mm)		
<35	4	8.7%
35–55	11	23.9%
>55	31	67.4%
Simpson grading		
1	26	56.5%
2	15	32.6%
3	4	8.7%
4	1	2.2%
Histopathology		
Transitional	24	52.17%
Fibroblastic	10	21.7%
Meningothelial	9	9.57%
Psammomatous	3	6.52%

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