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Recurrence-associated chromosomal anomalies in meningiomas: Single-institution study and a systematic review with meta-analysis

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ABSTRACT

Complete removal of a meningioma (MG) does not guarantee relapse-free survival. Alterations on several chromosomes responsible for MG recurrence were suggested, although their role was not validated by a systematic review. Following the analysis of own 161 cases, all previously published data has been collected for evidence synthesis. Based on own series, WHO grade >I (odds ratio (OR) = 92.0; 95%CI: 19.1–443.5) and a combination of loss of heterozygosity (LOH) on 1p and 14q (OR = 10.2; 95%CI: 19–55.7) were the independent recurrence-specific prognosticators. The deleterious role of LOH on 1p/14q was demonstrated in a subset of parasagittal and falcine MGs. A total of 742 cases and 10 studies were pooled for the Individual Patient Data and Aggregate Data models of meta-analysis, respectively. The prognostic role of WHO classification (OR = 90.4) and anomaly of chromosome 14 (OR = 3.5) was confirmed. LOH on 14 showed lesser impact on recurrence than suggested by the WHO grading (area under the curve 0.65 for LOH vs. 0.74 for WHO). Fixed effect model of meta-analysis provided high summarized OR values for 1p (OR = 5.4; 95%CI: 3.6–8.1) and 14q (OR = 7.6; 95%CI: 4.3–13.6), and low for chromosome 22 (OR = 1.6; 95%CI: 1.1–2.4). Final appraisal of recurrence-associated chromosomal alterations indicated that arms 1p and 14q deserve attention while predicting MG recurrence.

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1. Introduction

Meningiomas (MGs) are the most frequent intracranial tumour, accounting for up to 30% of the neoplasms in that location. Although most of them are slow-growing, solitary and benign tumours, their aggressive biological behaviour has been reported [1–3]. These tumours are regarded by experienced surgeons as easy to manage, however their complete removal is occasionally precluded due to the vicinity of vital structures. Even after total resection, about 3–10% of MGs relapse [4] and a less favourable prognosis is attributed to younger age, malignant histology and unnoticed brain invasion [1,5–8]. The World Health Organization (WHO) classification has facilitated estimating the prognosis [2,3,5,6,9]. In addition to the WHO classification, histopathological findings such as Ki-67/MIB-1 labelling index and proliferating cell nuclear antigen can independently predict the behaviour of a MG [3,10].

The molecular basis of MG's malignant behaviour has been recently scrutinized. A broad array of genetic alterations has been suggested, including complete or partial chromosome loss or gain, gene mutation and methylation [1–4,6,7,10–19]. Concerning the karyotype level, allelic loss of heterozygosity (LOH) on chromosomes 1, 6, 10, 14, and 22 has been postulated to increase the risk of malignant behaviour of sporadic MGs [2,4,11–13,15,18,20,21]. Beyond the deleterious role of a single anomaly, various configurations of LOH on several chromosomes were attributed to more aggressive phenotype of MG [4,12]. Most studies associated molecular aberrations with tumorigenesis, increased replication rate, histological progression or a higher WHO grade, occasionally focused on tumour recurrence [4,11,16]. According to Lee, who collected the largest cohort, the arm losses of 6q and 14q were the most reliable indicators of the MG relapse [4]. The previously published case series rarely exceeded 100 specimens, the investigators evaluated non-replicated chromosomal alterations and/or utilized completely different clinical endpoints. As of yet, genetic exams in MGs have not been applied in routine clinical practice. Moreover, dispersed molecular findings were never summarized in a systematic review. For these reasons, the molecular biology of MGs seems unjustly underappreciated while the development of a recurrence-specific genomic landscape seems feasible [16].

The aim of our study was to gather all the previous reports of MG-specific chromosomal alterations in order to extract reliable prognostic molecular biomarkers.

2. Material and methods

2.1. Study design

This study evaluated the impact of chromosomal alterations in sporadic MGs on recurrence. Following the identification of chromosomal arm losses in the entire own series of MGs, the individual features of tumour recurrence pooled including all accessible data from the existing literature and using PRISMA methodology. (For details – see 'Systematic Review methodology' in the electronic supplementary materials.)

2.2. Own series

The diagnosis of sporadic non NF1/NF2-related intracranial MG was based on the contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI) of the head, followed by histopathological examination. Following the approval of the local Bioethics Committee a total of 136 MGs of various intracranial locations were collected prospectively since 2002. All consenting patients were managed operatively at two neurosurgery departments (institution name deleted for peer-review purposes), gross total resection was intended in all of them. Basic demographics included patient age, sex and MG location. The Simpson grading for the extent of the tumour removal was utilized, though sparsely reported. The resection rate was not analyzed because it did not adhere to the RANO criteria for volumetric tumour remnant assessment [22]. The majority of patients were followed-up (121 of 136; 89.0%), however the follow-up time was not standardized. As the time to remote postoperative brain imaging was not established in the protocol, both the follow-up and time to recurrence were not valid for the statistical analysis. All tumour specimens were classified as grade I, II or III according to the World Health Organization (WHO) criteria, relevant to the year of assessment [9,23]. (For details – see 'Loss of heterozygosity analysis' in the electronic supplementary materials.)

During the surgery for the MG recurrence, the tissues were biopsied only for pathology and the genetic evaluation was skipped. A subgroup of recurrent MGs of parasagittal and falcine locations was selected throughout the entire group to demonstrate the recurrence-associated chromosomal anomalies, such as the 1p/14q alteration.

2.3. Systematic review and meta-analysis

For details – see 'Systematic Review methodology' in the electronic supplementary materials.

3. Results

3.1. Own series

Our study group consisted of 161 patients, (104 females, 64.6% and 57 males, 35.4%) diagnosed with MG. Their mean age was 56.1 (SD $\pm$ 14.5; min–max 22–92). The study group consisted of a total of 161 patients harbouring meningiomas. 104 of our patients were female (64.6%), and 57 were male (35.4%). 138 of the resected tumours were WHO grade 1 (85.7%), 22 were grade 2 (13.7%) and only one was grade 3 (0.6%). Of the entire cohort, a total of 35 meningiomas (21.7%) recurred during follow-up. (As noted in Methods, the follow-up time was not measured nor standardized.) As suspected, tumour recurrence strongly depended on the WHO grade ($p < 0.01$), specifically; 10.1% grade I (14 of 138), 90.9% grade II (20 of 22) and 100% (1 of 1) of grade III tumours relapsed. Among the determined set of loci, the recurrence rate was significantly greater when chromosome arms 1p (cytoband 1p33-32.3;), 14q (14q32.33) or 22q (22q11.23) were affected. On the contrary, LOH on chromosome arms 9p

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