Value of the proliferative and hormonal markers in estimation of biological behaviour of meningioma

KEYWORDS: Meningioma; Immunohistochemistry; Ki-67 Antigen; Steroids

INTRODUCTION

Meningiomas are common (13-26% of all primary intracranial neoplasms), usually benign slow-growing neoplasms of the central nervous system (1). However, some meningiomas can display aggressive behavior characterized by invasion of the brain, dura, and adjacent bone, multiple recurrences and a fatal outcome. While, the majority of meningiomas have distinct morphologic features that permit reliable diagnosis and classification (WHO grade I - benign, grade II - atypical and grade III - malignant s. anaplastic) by conventional histologic technique, some variants of meningioma, however, may raise the problems in assessing their prognosis. Although histological features may indicate the malignant nature of the neoplasm, they do not always correlate with patient outcome, since 2.3% to 30% of histologically benign meningiomas recur following macroscopically complete surgical removal (2). Recurrence is often accompanied by a more aggressive profile of histopathology and biologic activity. High mitotic index has been generally considered to be a strong indicator for tumor recurrence, but even this claim has been challenged (1). The risk of recurrence in the individual patient and the biological behavior of meningiomas can not be predicted by histology alone. In efforts to identify tumors with more aggressive clinical behavior, a number of authors have investigated the association of meningioma recurrence with histological features, as well as with data obtained from a variety of techniques which have been developed to evaluate cell proliferation (3,4). Hormonal (presumably progesterone) receptor status has also been correlated with recurrence of meningioma (5).

In this paper we want to indicate the present opinion about impact of proliferative and hormonal markers in estimation of biological behavior of meningiomas.

PROLIFERATIVE MARKERS

In an attempt to determine more precisely the correlates of aggressiveness and growth of meningiomas, researches have developed quantitative methods of measuring the proliferative activity (kinetics) of meningioma cells including: thymidine labeling, bromodeoxyuridine incorporation, nuclear organizing region analysis, histone in situ hybridization, telomerase activity, flow cytometric analysis and immunohistochemical markers. Among these techniques, immunohistochemical based markers such as PCNA and Ki-67/MIB-1 are widely used, because they are relatively easy to perform, they are fairly inexpensive and can be performed in a reasonably short period of time (3). Ki-67 antibody is more sensitive cell proliferation marker than PCNA. The antigen associated with Ki-67 antibody is encoded by a gene situated on chromosome 10. The antigen is present in the nuclei of cells in the G1, S, G2 and M-phases of the cell cycle, while, resting cells in the G0 phase do not express the Ki-67 antigen. By convention, and similar to mitosis counting, counts are usually performed in the area with the strongest immunostaining. The Ki-67 proliferation or labeling index (LI) is defined as the percentage of positively immuno-reactive tumor cell nuclei. This method (as well as mitosis counting) is subject to limitations associated with tumor heterogeneity and interobserver variability. The most authors reported that the distribution of the Ki-67 positive cells is heterogeneous in high-grade tumors, while, a more diffuse pattern is usually described in low-grade meningiomas (5).

There are significant increasing values of Ki-67 LI between tumor grades, from benign (mean 3.8% ± 3.1), over atypical (mean 7.2% ± 5.8) to anaplastic meningiomas (mean 14.7% ± 9.8). Differences in the mean Ki-67 LI between groups are statistically significant. However, Ki-67 LI, may vary considerably among anaplastic meningiomas (1.3 - 24.2%) (1), and there is also some overlap in Ki-67 LI ranges between different groups (6), which is important for interpretation of an individual Ki-67 LI in a given tumor. This interpretation must be done with caution, because a low Ki-67 LI does not necessarily imply a tumor without aggressive potential. The low LI may represent a sampling phenomenon. Evaluation of Ki-67 antibody is particularly helpful in cases that are histologically graded as "borderline". In these cases, high labeling index may suggest that the meningioma may be potentially more aggressive in terms of behavior (3). On other side, some authors believe that Ki-67 antibodies have no advantage over counting mitoses to assess proliferative activity in meningioma (6). Mitotic activity is included as a criterion of malignancy in the latest WHO version for meningioma grading (1).

HORMONAL MARKERS

During the last two decades much attention has been paid in the literature to the endocrine influence on meningiomas. This is supported by their higher incidence in women and the facts that meningiomas may wax and wane with pregnancy, and that they are positively associated with breast cancer. These observations opened the door to investigation of the role of sex hormone receptors in the growth of meningiomas and to a greater understanding of the pathways that control the expression and function of these receptors (7).

Approximately two-thirds of meningiomas express progesterone receptors (PR), with a higher fraction in meningiomas from female patients (7). It is unknown, however, how PR expression is regulated, especially since estrogen receptors (ER) are virtually absent in these tumors.

Although PR status was recently suggested to be an independent prognostic variable (5), this marker is also closely linked with histological grade. Expression of PR is associated with benign histology. Progesterone receptors are more frequently detected in meningothelial meningiomas than in other types, especially the atypical or malignant meningiomas (1). Atypical or anaplastic tumors frequently lack progesterone receptors (8). Progesterone receptor-negative meningiomas tend to be larger than progesterone-receptor-positive tumors.

Some recent data indicate that clinical factors, such as age, sex, tumor location and menopausal status, do not seem to correlate with progesterone receptor status (7). Progesterone receptor status has also been correlated with recurrence. Absence of progesterone receptors in meningiomas, together with a mitotic index greater than 6/10 high power fields, and malignant tumor grade, are highly significant predictors for shorter disease-free inter-
vals in meningiomas and poor outcome.

CONCLUSION

Although the proliferative markers and hormonal (progesterone) receptor status of meningiomas seem to provide useful, convenient, and predictive criteria for the subsequent evolution of the tumor, they should be used only in combination with other established histopathological features of tumor malignancy (cellular density, nuclear pleomorphism, necrosis and microcystic necrosis - especially multifocal microcystic). A simple, reproducible clear set of criteria for the tendency of a meningioma to recur is yet to be determined. In the last few years there are some new data concerning genetic characterization of meningiomas (9) and some cellular proteins (p53, p21, p27) (10) in meningioma cells which may be valuable in precisely discriminating atypical meningiomas from benign or anaplastic meningiomas, at least in histologically borderline cases.

REFERENCES


Tatjana STOŠIĆ-OPINČAL
Vesna PERIĆ
Mihail GAVRILOV
Svetlana GAVRILOVIĆ

CENTER FOR MAGNETIC RESONANCE, CLINICAL CENTER OF SERBIA

Fluid-attenuated inversion-recovery MR sequence in the evaluation of low-grade astrocytomas

KEYWORDS: Astrocytoma; Magnetic Resonance Imaging

INTRODUCTION

Low-grade astrocytomas are a heterogeneous group of intrinsic central nervous system neoplasms that share certain similarities in their clinical presentation, radiologic appearance, prognosis and treatment. These tumors are slow growing and patients survive much longer than those with high-grade gliomas do. According to the World Health Organization scheme, these tumors are grades I and II based on the histopathologic evaluation of surgical specimens. Therapeutic approaches for these tumors differ considerably according to grade, including partial or total resection or biopsy to make a histological diagnosis prior to consideration of radiotherapy (1,2). The development of neuroradiologic imaging techniques, which allow accurate determination of the grade, helps in better treatment planning and management.

MRT is an important in diagnosis, therapy planning and follow-up of cerebral tumors. It provides excellent detail, both of the anatomy of the lesion and often of its pathophysiology. Pathological features detectable by MRI include presence of cysts, necrosis, hemorrhage, edema and blood-barrier disruption. Follow-up of tumors conventionally involves T2-weighted (T2W), proton density-weighted (PD) and T1-weighted (T1W) imaging, before and after intravenous contrast medium. Typically, on T1W sequences, low-grade astrocytomas demonstrate same or decreased signal compared to surrounding brain. On T2W sequences higher signal reflects both the tumor and surrounding edema. T2W sequences are widely accepted as the most sensitive MR sequence for detection and delineation of glioma. Whist these tumors do not usually enhance initially, progression to a higher grade tumor is often accompanied by the appearance of focal areas of enhancement (3).

CHARACTERISTICS OF FLUID-ATTENUATED INVERSION-RECOVERY MRI SEQUENCE

Fluid-attenuated inversion-recovery (FLAIR) MRI sequence is one of inversion-recovery sequences that are used in diagnosis of many pathologi-