Journal of Neurological Sciences [Turkish] **23:(4)**# 9;279-286, 2006
http://www.jns.dergisi.org/text.php3?id=120

Research Article

Proliferative Indices (MIB-1) in Meningiomas: Correlation With The Histological Subtypes and Grades

Pınar KARABAĞLI[1], Aydın SAV[2]
[1]Meram Eğitim ve Araştıma Hastanesi, Patoloji Laboratuarı, Konya, Türkiye [2]Marmara Üniversitesi Tıp Fakültesi Nörolojik Bilimler Enstitüsü , Patoloji Laboratuarı, İstanbul, Türkiye

Abstract

We examined the proliferative potentials of meningiomas in 87 patients using the MIB-1 antibody against the Ki-67 antigen and compared them with the histopathologic subtypes and grades. Values of MIB-1 labeling indices (LIs) seem to parallel degree of histologic malignancy in many tumors, including meningioma. The growth potential of meningiomas is variable. MIB-1 LI of meningiomas is correlated with regrowth potential and tumor doubling time. In our study, histological grading of the meningiomas according to the latest World Health Organization clasification included the cases of 49 grade I, of 31 grade II, and of 7 grade III. The mean ± SD MIB index was 2.23±2.31 in grade I meningiomas, and those of grade II and grade III meningiomas were 6.53±5.31 and 11.1±7.8, respectively. There was a correlation between the values of MIB-1 LI and the histological grades. Meningiomas have also a wide range of histopathological appearances. Some differences for MIB-1 labeling indices were found among the subtypes of meningiomas of same grade. Results were analyzed using statistical methods and discussed.

Keywords: Meningioma, histologic grade, histologic subtypes, Ki-67, MIB-1, labeling index

Meningiomalarda Proliferatif MIB-1 İndeksi:Histolojik Alt Tipler ve Dereceleri ile İlişkisi

Özet

87 hastada meningiomaların proliferasyon potansiyelerini Ki-67 antijenine karşı MIB-1 antikoru kullanarak inceledik ve bu değerleri, meningiomaların histopatolojik alt tipleri ve dereceleri ile karşılaştırdık. MIB-1 bağlanma indeksi, meningioma dahil birçok tümörde histolojik olarak malignite derecesi ile parallel gibi görünmektedir. Meningiomalarda büyüme potansiyeli farkılıklar gösterir. MIB-1 bağlanma indeksi meningiomalarda tümörün yeniden büyüme potansiyeli ve tümör ikiye katlanma (doubling) zamanı ile koreledir. Çalışmamız histolojik olarak en son Dünya Sağlık Örgütü dereceleme sistemine (2000) göre 49 adet derece I, 31 adet derece II ve 7 adet derece III meningioma olgusu kapsamaktadır. Derece I meningiomalarda MIB-1 bağlanma indeksi 'ortalama ± standart sapma' değeri 2.23±2.31 iken, derece II ve derece III meningiomalarda sırası ile 6.53±5.31 ve 11.1±7.8 bulundu. MIB-1 bağlanma indeksi değerleri ve histolojik dereceleri arasında ilişki saptandı. Meningiomalar geniş bir histopatolojik görünüm spekturumuna da sahiptirler. Aynı derecede olmalarına rağmen meningioma olgularının histopatolojik alt tipleri arasında, farklı MIB-1 bağlanma indeksleri saptandı. Sonuçlar istatistiksel yöntemler ile analiz edilerek tartışıldı.

Anahtar Kelimeler: Meningioma, histolojik derece, histolojik alt tipler, Ki-67, MIB-1, bağlanma indeksi

INTRODUCTION

Measurement of tumor cell proliferation yields very valuable data for the analysis of central nervous system (CNS) tumors, and markers of cellular proliferation have become widely used in them. These include counting mitotic figures, and more informative techniques such as cell-cycle analysis by flow cytometry, computerized image analysis or immunohistochemistry

using bromodeoxyuridine, PCNA and Ki-67 antibodies [3,5,8,9,31]. The nuclear antigen Ki-67 is, perhaps, the most widely used proliferation marker because of its applicability to paraffin sections and lack of major technical concerns [3,5,8,12,23]. Ki-67 is an antigen expressed in all phases of the cell cycle excluding the G0 phase [5,6,9,11,23,29,31]. The MIB-1 monoclonal antibody has been used frequently to stain Ki-67 antigen, which is present in all proliferative cells, in order to investigate the growth potential of various systemic and intracranial neoplasms [21].

Values of MIB-1 labeling indices (LIs) seem to parallel degree of histologic malignancy in many tumors, including glioblastoma multiforme, anaplastic astrocytoma, pituitary adenoma, and meningioma [3,23]. Meningioma is one of the most common among brain tumors. It is usually benign in nature and arises from the arachnoid cells or the arachnoid membrane covering the brain [17,22,23]. The growth potential of meningiomas is variable. Some meningiomas remain unchanged in size for a long period of time, whereas others grow rapidly [22]. The WHO has graded meningiomas into three categories: Grade I, Grade II, and Grade III [19] Some investigators have reported that histologic grade was significantly correlated with MIB-1 LI [11,13-15,25].

Meningiomas have a wide range of histopathological appearances. The subtypes share immunohistochemical and ultrastructural characteristics. Of the various subtypes, meningothelial, fibrous and transitional meningiomas are by far the most common [19]. Some differences for MIB-1 labeling indices could found among the subtypes of meningiomas of same grade.

As MIB-1 LIs would reflect tumor proliferating potential, the high levels of which represent increased tumor proliferation, MIB-1 LI also was correlated with recurrence [7,10,25,33]. Assesment of the growth fraction in meningiomas by immunostaining with Ki-67 could become an important tool in the prediction of the biological behaviour of nervous system neoplasms and the planning of adjuvant therapy [23] The MIB-1 LIs in surgical specimens of meningiomas were examined and compared with the histopathologic subtypes and grades.

METHODS

In this study, 87 meningiomas were drawn from the archives of the Pathology Laboratory, Marmara University Institute of Neurological Sciences from 1995 to 2003. Hematoxylin-and-eosin slides of the cases were reviewed by two observers (AS, PK), and the tumors were categorized into subtypes of meningioma according to the latest WHO classification [19].

One representative tissue block was selected for each case. 5µ sections of routinely processed paraffin blocks were mounted on 3- aminopropyl-triethoxysilane-coated slides and thoroughly dried at room temperature for one night. Slides were deparaffinized and rehydrated through graded alcohols. Antigen retrieval was performed by using 0,1 mmol/L citrate buffer in a microwaveable pressure cooker and boiled in microwave oven for 15 minutes. Slides were incubated in 3% hydrogen peroxide/methanol for 20 minutes to block nonspecific backround staining due to endogenous peroxidase. Using the standart streptavidin-biotin peroxidase complex (SABC Link, Lab Vision) method, Ki-67 (MIB-I, Neomarkers, Fremont, CA, USA) was performed on all slides. The slides were incubated for 30 minutes in secondary antibody solution. Diaminobenzidine (DAB) (Lab Vision, TA-125-HD) served as the chromogen. The samples of lymph node was used as positive control for MIB-1, respectively. Negative control was produced with the same tumor samples and staining methods by omitting the primary antibody.

Each slide was scanned at low power, and the area that appeared to have the highest density of labeled nuclei (hot spot) was selected for counting at a magnification of X400. Minimum 1000 cells were counted except inflammatory and vessel cells for each sample. The ratio of positive staining nuclei to the total number of tumor cells was indicated as an MIB-I LI percentage. Nuclear staining were evaluated independently from their staining intensity. Values were statistically calculated as median and mean ± standart deviation by using Microsoft Excel computer software.

RESULTS

Histological grading of the meningiomas according to WHO-2000 grading system included cases of 49 grade I, 31 of grade II, 7of grade III. In all cases, MIB-1 immunoreactivity was confined to the nuclei. MIB-1 nuclear positivity usually had a coarsely granular or clumped appearence. In our study, there was a correlation between the values of MIB-1 LI and the histological grades. The correlation of tumor grades and MIB-1 LIs is summarized in Table 1. In general, cellular proliferation proportionately increases from benign to atypical and to anaplastic meningioma. In malignant meningiomas, MIB-I LI values were much higher than grade I meningiomas. Histological diagnosis, the number of cases, distribution of range, mean ± standart deviation (SD) and median values of MIB-I LI according to the histopathologic subtypes are summarized in Table 2.

Table 1: The association of grades to MIB-I LI.

Grade	Number of cases (n)	MIB-I LI Median(Range)	MIB-I LI Mean ± SD
I	49	1.4 (0-11)	2.23 ± 2.31
II	31	5 (0-19.9)	6.53 ± 5.31
III	7	12.6 (1.7-25)	11.1 ± 7.8

Table 2: Summary of labeling indices by histological subtypes.

Subtype	Number of cases (n)	MIB-I LI Median(Range)	MIB-I LI Mean ± SD	WHO Grade
Meningothelial	31	1.4 (0-11)	2.21 ± 2.51	I
Fibrous	5	0.9 (0-4)	1.28 ± 1.57	I
Transitional	6	4.25(0-5.8)	3.29 ± 2.48	I
Psammomatous	1	0.9		I
Microcystic	3	1.4 (1-5.0)	2.46 ± 2.2	I
Secretory	3	1.9 (0.9-3.4)	2.06 ± 1.25	I
Clear cell	2	5.84 (1.68-10)	5.84 ± 5.88	II
Chordoid	4	8.5 (3.1-15)	8.77 ± 5.86	II
Atypical	25	5 (0-19.9)	6.22 ± 5.34	II
Papillary	2	5.2 (1.7-8.7)	5.2 ± 4.94	III
Rhabdoid	1	12.6		III
Anaplastic	4	13.35 (3.0-25)	13.67± 8.99	III

Of 49 grade I meningiomas, there were 31 meningotheliomatous, 5 fibromatous, 6 transitional, 1 psammomatous, 3 microcystic, and 3 secretory meningiomas. MIB-I LI ranged from 0% to 11% (mean ± SD, 2.23 ± 2.31) within total 49 tumors (Fig 1). MIB-I LI in the transitional meningiomas were higher than other grade I meningiomas. Of 31 grade II meningiomas, there were 2 clear cell, 4 chordoid, and 25 atypical meningiomas. MIB-I LI ranged from 0% to 19.9% (mean ± SD, 6.53 ± 5.31) within grade II meningiomas (Fig 2). MIB-I LI in the chordoid meningiomas were higher than clear cell and atypical meningiomas. Of 7 grade III meningiomas, there were 2 papillary, 1 rhabdoid, and 4 anaplastic meningiomas. MIB-I LI ranged from 1.7% to 25% (mean ± SD, 11.1 ± 7.8) within grade III meningiomas (Fig 3-4). MIB-I LI in anaplastic meningiomas were higher than the other subtypes of meningioma.

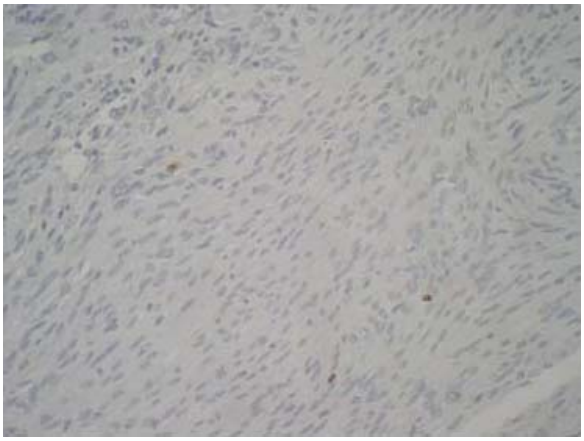

Fig 1: *MIB-1 immunostaining in a grade I, fibroblastic meningioma with MIB-1 LI of 1% (MIB-1 antibody x400).*

Fig 3: *MIB-1 immunostaining with the regional variability of LI within a grade III, anaplastic meningioma (MIB-1 LI = 25%) (MIB-1 antibody x100).*

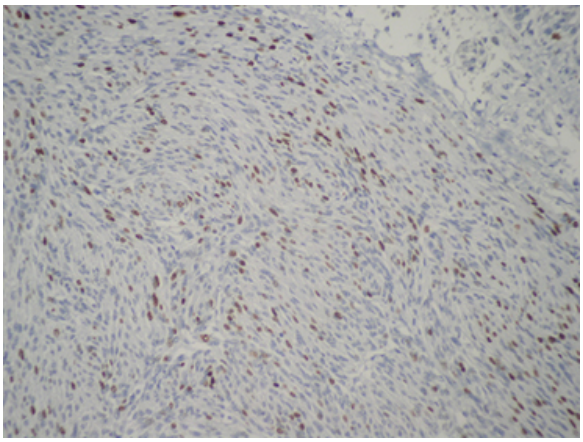

Fig 2: *MIB-1 immunostaining in a grade II, atypical meningioma with MIB-1 LI of 10% (MIB-1 antibody x200).*

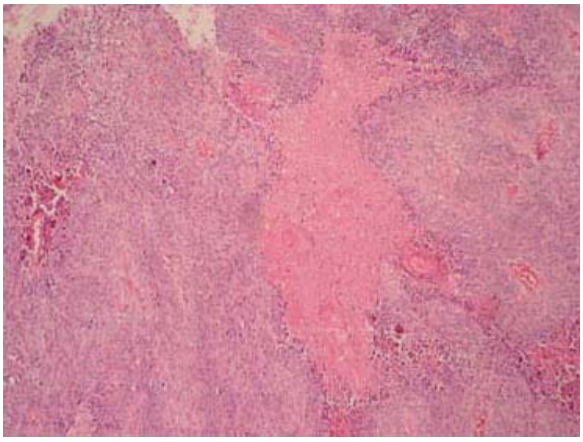

Fig 4: *Grade III, anaplastic meningioma demonstrating necrosis, mild nuclear pleomorphism with MIB-1 LI of 25% (hematoxylin-eosin x100).*

DISCUSSION

Subjective methods such as mitotic index, necrosis, etc. are still used in determining the grade and proliferating activity of CNS tumors. However, interobserver differences and sampling errors usually cause problems. Ki-67 MoAb analysis by immunohistochemistry is widely used because of its applicability to paraffin sections and giving possibility to retrospective analysis [5,8,12,23,32]. The proliferative potential of meningiomas has been studied using the Ki-67/ MIB-1 immunohistochemistry in several studies.

Nakasu et al. reported that the mean Ki-67LI was 0.9±6,43% in three anaplastic meningiomas, and that of atypical and benign meningiomas was 2.75±1.43 (n=10) and 1.06±0.63% (n=107), respectively [22]. Shibata et al. examined 13 meningiomas; the mean Ki-67 index was 1%, but rose to 5% in recurrent and anaplastic meningiomas [30]. Karamitopoulou et al. reported that the mean MIB-1 LI values ± SD were 1.3±3.3% for the benign, 9.3±6.9% for atypical, and 15.0±16.9% for the anaplastic meningiomas [11]. Kolles et al. reported that Ki-67(MIB-1) LI is the most important criterion for distinguishing anaplastic meningiomas (WHO grade III) (mean Ki-67 index:11%) from those of common type (WHO grade I) (mean Ki-67 index:0.7%). The atypical meningiomas (WHO grade II) are characterized by a mean Ki-67 LI of 2.1% [13]. Lamszus et al. found a correlation between the MIB index and WHO grade. The average MIB index was 5.71±3.73 in 40 grade I meningiomas, and the mean MIB index of grade II and grade III meningiomas were 10.01±4.10 (n=21) and 15.66±12.64 (n=8) [14]. Amatya et al. reported that the mean MIB-1 LI was 1.5% in 109 benign meningiomas. In contrast, the anaplastic meningiomas had a high MIB-1 LI (mean 19.5%). The atypical meningiomas had MIB-1 LIs in the range between benign and anaplastic meningiomas (mean 8.1%) [2] Ozen et al. reported that the mean MIB-1 LI values for the grade I and grade II meningiomas were 1,1% ad 2,3%, respectively [25]. Most recently Roser et al reported a large retrospective study of 600 resected meningiomas in which histological grading revealed 91% WHO grades I meningiomas (mean MIB-1 LI: 3.88%), 7% WHO grades II meningiomas (mean MIB-1 LI: 9.95%) and 2% WHO grades III meningiomas (mean MIB-1 LI: 12.18%)[26].

In our study, the mean ± SD MIB index was 2.23±2.31 in grade I meningiomas, and those of grade II and grade III meningiomas were 6.53±5.31 and 11.1±7.8, respectively.

There was a correlation between the values of MIB-1 LI and the histological grades although MIB-I LI was of different values in different series according to the gradual differences among series. Grade III meningiomas were higher than the other grade I and grade II meningiomas in accordance with other studies.

The problem with LIs is the regional variability within a tumor, as well as the variability within a tumor grade (Grade I as high as 11% and Grade III as low as 1.7%) (fig 3). Issues of tumor heterogeneity and sampling are important to consider. The recorded MIB-1 LI should be determined in the area of the meningioma with the highest degree of positive staining, since it is this particular area that theoretically determines the proliferative potential of the tumor. However, finding the area that has the highest proliferative activity will depend on thorough sectioning and staining, which even when adhered to may not detect a minute focus of cells with a high proliferation rate. A slide chosen for purposes of cell proliferation immunohistochemistry may or may not represent the most proliferative area of a given tumor. On the other hand, surgically removed tissue samples may not represent

the most proliferative area of a given neoplasm. Moreover, there appears to be overlap in terms of rangers of labeling indices at the interface between tumor grades. All of these issues should cause one to be cautious in the interpretation of labeling indices. Despite all these limitations, cell proliferation markers may be useful in selected circumstances[1,5,31,32].

Lamszus et al. also examined the MIB index of some grade I meningioma subtypes. The mean ± SD MIB index of meningothelial, transitional, fibrous, angiomatous and microcystic meningiomas were 4.99±2.95 (n=16), 6.19±3.57 (n=10), 6.62±5.04 (n=10), 5.75±3.04 (n=3) and 1.60±0.00 (n=1) (12). Colakoglu et al. reported that the Ki-67 LI was 0.3% in secretory meningiomas[4].

In our study, the mean ± SD MIB-I LI values were 2.21±2.51 (n=31) in meningothelial type, 1.28±1.57 (n=5) in fibrous type, 3.29±2.48 (n=6) in transitional type, 2.46±2.2 (n=3) in microcystic type and 2.06±1.25 (n=3) in secretory type meningiomas (Table 2).

Rushing et al. reported that the MIB-1 LI of atypical meningiomas ranged from 3-19%, mean 12%, and from 5.5-17.5%, mean 11.75% for papillary meningioma[27].

In our study, MIB-I LI ranged from 0% to 19.9% (mean±SD, 6.53 ± 5.31) within grade II meningiomas. The mean ± SD MIB-I LI values were 6.22±5.34 (n=25) in atypical type, 8.77±5.86 (n=4) in chordoid type, 5.84±5.88 (n=2) in clear cell type meningiomas (Table 2). MIB-I LI in the chordoid meningiomas were higher than clear cell and atypical meningiomas.

Kayaselcuk et al. reported that the mean Ki-67 LI value was 33.12±29.39 in their four cases of anaplastic meningioma group [12].

In our series, MIB-I LI ranged from 1.7% to 25% (mean±SD, 11.1 ± 7.8) within grade III meningiomas. The mean ± SD MIB-I LI values were 13.67±8.99 (n=4) in anaplastic type, 5.2±4.94 (n=2) in papillary type and MIB-I LI was %12.6 (n=1) in rhabdoid type meningiomas (Table 2). MIB-I LI in anaplastic meningiomas were higher than the other subtypes of meningioma.

Matsuno et al. reported that higher MIB-1 LIs were observed for younger patients [20]. In another study, Sandberg et al. reported that the median MIB-1 LI for pediatric meningiomas without histological atypia did not differ significantly from for adult meningiomas without histological atypia[28].

Some authors have found a higher mean MIB-1 LI in meningiomas that ultimately recurred, while others have obtained different result. Yamasaki et al. reported that the MIB-1 LI ranged from 0.01% to 8.7% (mean±SD, 2.0±1.8) of the total 54 meningiomas. MIB-1 LI values of the initial specimens of recurrent tumors (4.3±2.7) were higher than the nonrecurrent tumors (2.0±1.8). Recurrence was seen in 6 meningiomas and all of them were meningothelial subtype. In that study, MIB-I LI was correlated with recurrence [33]. Lanzafame et al found that correlation between MIB-1 LI, histological grade, and follow-up was significant. In the recurrence group MIB-1 LI significantly higher than in the disease free group. It was significant higher in recurrent histologically benign meningiomas, as compared with benign meningiomas without recurrence [16]. Caroline et al. found no statisticaly significant difference between MIB-1 LIs in recurrent and nonrecurrent meningiomas, although there was a higher mean MIB-1 LI in the group of meningiomas that ultimately recurred (MIB-1 LI=5.4) compared with those that did not (MIB-1 LI=1.5). There was an extensive amount of overlap in the MIB-1 LI ranges observed these two groups [1]. Tyagi et. al. reported that the extend of surgical excision and histology are the two major factors that have any influence in prediction of risk of recurrence; MIB-1 LI is not helpful[31].

The higher values of MIB-1 LI in subtypes of low grade meningiomas may be due to possible recurrence potential of the tumors. As we have not selected the recurrent and nonrecurrent cases in our study, our results may differ from the other studies.

There are sufficient differences in terms of staining technique and interpretation for a given stain that comparison of indices needs to be done within the known parameters of a given laboratory. In the words, a labeling index of 5% in one laboratory may not necessarily translate into a labeling index of in another laboratory [32].

CONCLUSION

There was a correlation between the values of MIB-1 LIs and the histological grades. In final analysis, LIs of grade III meningiomas were higher than that of the grade I and grade II meningiomas. A very high labeling index in a tumor that morphologically appears to be either low or intermediate grade, may be used as an evidence in support of a higher grade lesion. Low labeling indices tend to be less helpful in predicting biological behaviour of the tumor under investigation. In addition, there appears to be somewhat overlaps in terms of wide range of labeling indices at the interface between tumor grades.

Some differences for MIB-1 Lıs were found among the subtypes of meningiomas of same grade. In grade I meningiomas, transitional meningiomas is characterized by highest MIB LI whereas lowest scores are reflected by fibroblastic meningiomas. Recent classification proposed by WHO-2000 classifies chordoid, clear cell and and atypical meningiomas as grade II. Surprisingly, MIB-I LI in the chordoid meningiomas were higher than clear cell and atypical meningiomas. MIB-I LI in anaplastic meningiomas were higher than the other subtypes of meningioma.
MIB-1 LIs were of different values in different series according to the gradual differences among series although there were a correlation between the values of MIB-1 LI and the histological grades. However, as in our study indicated the due to wide varying LI values in different histological types of meningiomas, for the time being there is no reproducible and reliable LI cut-off levels for differentiation of these tumors. Until that time, each institution will need to determine its own prognostic cut-off values [2]. Despite all these limitations, cell proliferation markers may be useful in selected cases.

Correspondence to
Pınar Karabağlı
E-mail: pinarkarabagli@yahoo.com

Received by: April 23 2006
Revised by: September 16 2006
Accepted : September 27 2006

The Online Journal of Neurological Sciences (Turkish) 1984-2005
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
ISSNe 1302-1664

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