S100A5: a marker of recurrence in WHO grade I meningiomas

S. Hancq*, I. Salmon†, J. Brotchi*, O. De Witte*, H.-J. Gabius‡, C. W. Heizmann§, R. Kiss¶ and C. Decaestecker¶

*Departments of Neurosurgery and †Anatomopathology, Erasmus University Hospital, Brussels, Belgium, §Institute of Physiological Chemistry, Faculty of Veterinary Medicine, Ludwig-Maximilians-University, Munich, Germany, ‡Division of Clinical Chemistry and Biochemistry, Department of Pediatrics, University of Zürich, Zürich, Switzerland, and ¶Laboratory of Toxicology, Institute of Pharmacy, Université Libre de Bruxelles, Brussels, Belgium


S100A5: a marker of recurrence in WHO grade I meningiomas

Some WHO grade I intracranial meningiomas resected from the same sites and with the same quality of resection (Simpson’s grading scale) recur, while others do not. The reasons for this variability in occurrence of recurrence have not yet been determined. We therefore investigated the prognostic recurrence value of seven biological markers on a series of completely resected WHO grade I meningiomas. For this purpose, we analysed a series of 33 WHO grade I meningiomas totally resected between 1980 and 1990 (a follow-up of 10 years), including 14 cases of recurrence. The fixed tumour material from each meningioma was submitted to histochemical analyses targeting galectin-3 and its binding sites, the S100A5, S100A6 and S100B proteins, and cathepsin-B and -D. The levels of expression were assessed semi-quantitatively (in terms of the staining intensity and the labelling index) and submitted to uni- and multivariate analyses. Of all the markers investigated, only S100A5 expression can be associated with any significant prognostic value in the matter of recurrence. More particularly, the meningiomas with high levels of S100A5 staining intensity either did not recur, or recurred later than those with a low immunopositive S100A5 intensity ($P = 0.004$). Cox regression analyses demonstrated that this latter marker was associated with significant prognostic values independent of the patients’ ages. Furthermore, the combination of the patients’ ages and S100A5 staining intensity permitted the identification of a group with a particularly high risk of recurrence, that is, the patients younger than 55 and with meningiomas exhibiting low S100A5 intensities ($P = 0.001$). In conclusion, the S100A5 protein could play a role in the recurrence of totally resected WHO grade I meningiomas.

Keywords: cathepsin, galectin, meningioma, S100 proteins, tumour recurrence

Introduction

Meningiomas represent 15% of all intracranial tumours [1]. They arise in the arachnoid cap cells of the dura mater. Most of them are benign (and defined as grade I by the WHO classification), well circumscribed and slow-growing. However, some of these benign tumours can recur unexpectedly after surgical resection [2]. A clear distinction must be made between tumour recurrence and tumour regrowth. The term ‘recurrence’ must be reserved for meningiomas which reappear in the operative field after total macroscopic resection (Simpson grade 1 or 2) [1,3,4]. The recurrence rate for a totally resected WHO grade I meningioma located in the convexity is...
Recurrence in WHO grade I meningiomas

179

about 5%, with an average period of grace of 45 months [2].

As reported by different authors [1,2,5], the recurrence rates after 5, 10 and 20 years are around 6%, 13% and 25%, respectively. Previous studies have investigated different types of prognostic factors associated with the recurrence of meningiomas. However, the most significant predictors of recurrence are the quality of the surgical resection and the WHO grade scale [4,6–8]. In contrast, patients’ ages, sexes and the sizes and sites of their tumours, as well as histological subtypes within WHO grade I meningiomas, have not been demonstrated as being clear indicators of recurrence [3,4,6,9], and this has given rise to controversy [1,10]. For clarity, it should be noted that some histological types have a worse prognosis and correspondingly higher WHO grades. In the field of radiology, prognostic factors have also been proposed such as the time required for the volume of a tumour to double [6], the presence of a peritumoural brain oedema, or tumour shape evaluated by computerized tomography (CT) scanning [9,11].

Furthermore, in an attempt to prognosticate recurrence, a number of biological markers have been proposed for different tumour types. A first group of markers involves cell kinetics, for which a general consensus seems to have emerged on the basis of the fact that proliferative activity is significantly higher in malignant than in benign meningiomas [12–15]. However, whereas some authors have obtained significant results [14,16], neither we [15] nor certain others [12,13] have been able to demonstrate a statistically significant relationship between cell proliferation and meningioma recurrence.

Galectins, a family of calcium-independent glycoproteins, constitute a second group of markers. Galectins (in particular galectin-3) are potent elicitors of biosignalling and thereby involved in the cell proliferation, the migration and the invasive activity of various types of tumours, making them a target for therapy [17–21]. The expression of galectins and the roles that they play in tumours of the central nervous system are still poorly characterized. Together with other investigators, we also have evidenced a relationship between the levels of expression of galectin-3 and the progression of malignancy in human astrocytic tumours [22–25]. In contrast to astrocytic tumours, no data have been reported on galectin-3 expression in meningiomas – at least to our knowledge.

A third group of markers is made up of a family of calcium-binding proteins in the shape S100 proteins. These S100 proteins, which are found in different cell types – mainly nerve, glial and epithelial – are responsible for a large set of biological functions such as cell proliferation, apoptosis, motility, exocytosis and cytoskeletal organization [26,27]. Altered levels of S100 proteins have been found in many transformed cells, particularly in neoplasms, where both up- and down-regulation processes have been reported (for a review see [26]). We were the first to demonstrate that marked modifications to the levels of expression of different S100 proteins (including S100A5 and S100A6) occur in connection with the progression of astrocytic tumour malignancy [28,29]. To date, only the immunohistochemical expression of S100B has been investigated in meningiomas though only partly, and the results obtained are rather conflicting [30–33].

A fourth major group of biological markers playing major roles in tumour growth, recurrence and/or regrowth includes proteolytic enzymes, of which cathepsins, serine proteases and metalloproteases comprise the three major subgroups. Recently, Strojniki et al. [34] showed that levels of cathepsin-B and -L antigens are significantly higher in benign meningiomas presenting invasive behaviour patterns.

The aim of the present study is to test and compare some of these biological markers as predictors of recurrence in the case of totally resected WHO grade I meningiomas. We focused our attention on galectin-3 and its binding sites as well as on S100A5, S100A6 and S100B, and two cathepsins, that is, cathepsin-B (a cysteine protease) and cathepsin-D (a lysosomal aspartyl protease).

Materials and methods

Clinical data

In order to obtain homogeneous series, we retrospectively selected 33 intracranial primary meningiomas classified as grade I in terms of the WHO classification [35]. These cases were extrapial and fulfilled three conditions:

• The great majority of the patients had been operated on before 1990 with the total resection of their meningiomas (Simpson 1 or 2).
• Complete clinical data were available for each patient. Patients without recent follow-ups received a summons for a new radiological [CT scan or magnetic resonance imaging (MRI)] and neurological examination.
• There was enough material in good condition from each tumour to enable immunohistochemical stainings to be performed.

Of the 33 patients with WHO grade I meningiomas, 19 were without recurrence at the time of analysis (these constituted the $R^-$ group) and 14 showed recurrences (the $R^+$ group), as summarized in Table 1. Women predominated in both groups (23 F : 10 M). As detailed in the Results, the $R^+$ patients were younger than the $R^-$ ones.

Clinical symptomatology consisted of headaches, difficulties in walking, behavioural trouble followed by an affection of the cranial nerves, motor palsy, initial epilepsy and intracranial hypertension.

In the matter of preoperative diagnosis, the CT scan was the preferred type of examination carried out on the two groups. As MRI only appeared later, few patients had been submitted to it as part of the process of preoperative management.

The histopathological types included seven fibroblastic, 18 transitional, two angiomatous, three psammomatous and three meningothelial variants.

The meningioma sites in the $R^-$ group were the convexity ($n = 8$), the parasagittal area ($n = 5$), the falx ($n = 3$) and the skull base ($n = 3$). For the patients with recurrences ($R^+$ group, $n = 14$), the main tumour sites were the skull base ($n = 8$) followed by the falx ($n = 3$), the parasagittal area ($n = 2$) and the convexity ($n = 1$).

### Table 1. WHO grade I meningiomas: clinical data

<table>
<thead>
<tr>
<th>Variables</th>
<th>$R^-$ (non-recurrent)</th>
<th>$R^+$ (recurrent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Female/male</td>
<td>10/9</td>
<td>13/1</td>
</tr>
<tr>
<td>Patients’ ages (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–30</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>30–60</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Scan</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Angiography</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>MRI</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Tumour sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convexity</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Parasagittal</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Falx</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Base</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Range</td>
<td>1–13</td>
<td>1–14</td>
</tr>
</tbody>
</table>

### Specimen preparation: chemicals and reagents

Several paraffin blocks containing formalin-fixed tissues were available for each of the 33 meningiomas under study. One haematoxylin-eosin-stained histological slide was obtained from each block, and the block most representative of the lesion to be analysed was selected consensually by two neuropathologists. Thirty histological slides ($5 \mu m$ thick) were then taken from the block selected. The extent of the specifically bound antibodies was demonstrated by avidin-biotin-peroxidase complex (ABC) kit reagents (Vector Labs, Burlingame, CA, USA), with diaminobenzidine/$H_2O_2$ as the chromogenic substrates. Counterstaining with haematoxylin-eosin concluded the processing. For each of the immunostainings, a control reaction was carried out by omitting the incubation step with the primary antibody.

The immunohistochemical protocol used for the S100 antibodies was identical to that detailed recently [28]. Briefly, the dilutions used for the S100 antibodies were 1 : 500 for the S100A5, 1 : 10 000 for the S100A6 and 1 : 10 000 for the S100B. As characterized elsewhere [36,37], the three recombinant antihuman S100 sera were raised in rabbits (S100A5, S100B) and goats (S100A6). The staining patterns are illustrated elsewhere [28].

The expression of galectin-3 and its reactive sites were demonstrated by means of a specific polyclonal anti-galectin-3 antibody (1 : 100) and biotinylated galectin-3 (10 $\mu g/ml$), as detailed previously [23,24]. The control reactions included competitive inhibitions to ascertain sugar specificity, and the omission of the incubation step with the probe served to exclude any staining by the binding of kit reagents such as mannose-rich glycoproteins, horseradish peroxidase and avidin. Notably, specificity controls had ensured that the antibody had no cross-reactivity to other family members, especially galectin-1 and galectin-8. Counterstaining with haematoxylin-eosin concluded the processing. The staining patterns are illustrated elsewhere [23,24].

The protocol used to characterize the immunohistochemical expression of cathepsin-B and -D was identical to that described previously [38,39]. The antibodies used were a rabbit polyclonal antibody purified from human liver for cathepsin-B, and a mouse monoclonal antibody for cathepsin-D (Oncogene Research Products, CALBIOCHEM, Cambridge, MA, USA). The staining patterns are illustrated elsewhere [39].
Immunohistochemical analysis

The level of immunohistochemical expression of the different markers was semi-quantitatively evaluated, as previously detailed for the assessment of the various glycohistochemical markers in meningiomas [40] and the S100 proteins in another tumour type [41]. Two variables were taken into account, namely the staining intensity (SI) and the labelling index (LI); the latter refers to the percentage of meningothelial cells reacting to each probe. The SI variable was evaluated as negative (0), weak (1, i.e. not very different from the background evaluated on the negative control slide), moderate (2) and strong (3). The LI variable was also divided into four classes according to whether there was no labelling (0), or there were fewer than 33% (1), 34–66% (2) or more than 66% (3) of immunopositive tumour cells. To evaluate these variables, 10 microscopic fields (×200) were analysed. In the case of heterogeneity, 10 others were taken into account to determine the most prevalent SI and LI levels which was attributed to the specimen analysed.

Data treatment

Seven biological markers were analysed in the present study by means of two variables (SI and LI). This means that 14 variables were calculated for each of the meningiomas under study. Using standard Kaplan-Meyer analyses and Gehan’s generalized Wilcoxon test, we investigated the prognostic value of the markers concerned. We used a decision-tree-based technique [42,43] to help us to determine appropriate threshold values for performing these analyses. Standard Cox regression analysis was also used to test the possible simultaneous influence on the remission period of several variables. All the statistical analyses were carried out using Statistica (Statsoft, Tulsa, OK, USA).

Results

Different protein expression in recurrent and non-recurrent meningiomas

Figure 1 shows the most differentially expressed levels of expression of S100A5, S100A6 and cathepsin-D across the recurrent (black dots) and the non-recurrent (open dots) cases considered among the totally resected (Simpson 1 or 2) WHO grade I tumours. Either their LI (percentage of immunopositive cells, see S100A6) or their SI (see cathepsin-D), or indeed both (see S100A5), exhibited quite different value distributions across the recurrent and the non-recurrent cases. In Figure 1, relatively clear separations between the recurrent and the non-recurrent cases are illustrated by horizontal lines. A dotted line indicates that the separation is not so evident. However, as stated below, these separations have to be statistically confirmed. As morphologically illustrated in Figure 2, Figure 1 shows that most of the non-recurrent cases exhibited a high level of S100A5 expression (Figure 2B), that is, an LI and/or SI ≥2. In contrast, a large number of the recurrent cases showed a low level of S100A5 SI (≤1; as illustrated in Figure 2A). This discrimination is illustrated by the horizontal line in Figure 1. The S100A6 LI seemed able to distinguish between the recurrent and the non-recurrent cases. In contrast to the non-recurrent cases, the recurrent ones were mainly associated with a low percentage of immunopositive cells (≤1). Finally, high cathepsin-D immunostaining intensity (≥2) was more associated with recurrence than with non-recurrence. However, all these data display tendencies rather than any clear threshold values between the recurrent and the non-recurrent cases. More sophisticated analyses able to take into account the disease-free period of each patient were consequently performed (see the Kaplan-Meyer analyses reported below). We had already observed that the groups of patients formed on the basis of the S100A6- or cathepsin-D-related variables (separated by the horizontal lines in Figure 1) exhibited more heterogeneous remission distributions (i.e. disease-free periods) than the groups set up on the basis of the S100A5-related variables.

No interesting prognostic features were found for the other markers (cathepsin-B, galectin-3 and its binding sites and S100B). Briefly, while all the cases (both recurrent and non-recurrent) presented homogeneous labelling indices (i.e. low values in the case of S100B and high ones for the three other markers), low and high SI were encountered in both R+ and R− groups.

Prognostic value of S100A5, S100A6 and cathepsin-D for meningioma recurrence

We submitted the value distribution shown in Figure 1 to Kaplan-Meyer analyses in order to analyse the disease-free periods of the patients whose tumours exhibited either low
(≤ 1) or high (≥ 2) levels of expression. As shown in Figure 3, only S100A5 expression was able to generate significantly separate Kaplan-Meyer curves (describing the cumulative amount of recurrence-free cases). The separation between the two curves was estimated as being very significant for both the S100A5 LI (Figure 3a; \( P = 0.008 \)) and the immunostaining intensity (Figure 3b; \( P = 0.004 \)). The raw data shown in Figure 1 indicate that for both variables a high level of S100A5 expression (≥ 2) is of better prognostic value than a low level (≤ 1). However, immunostaining intensity appears to be a more satisfactory prognostic factor. Indeed, only one patient with a relatively short disease-free period (fewer than 10 years) was selected by the curve associated with a low risk of recurrence (see the arrow in Figure 3b) as opposed to the four cases selected if the LI was considered (see the arrows in Figure 3a). The curve associated with a low risk of recurrence in Figure 3(b) consequently indicates that 10 years after surgery, the remission rate was about 90% (against 75% in Figure 3a). In contrast, no S100A6- or cathepsin-D-related variable was able to generate any significantly different remission curves (data not shown). This was essentially owing to the heterogeneity of the recurrence-free periods shown by the cases allocated to the different groups set up on the basis of these variables (as already observed in Figure 1). We used a Cox regression analysis to test the simultaneous influence of S100A5, S100A6 and cathepsin-D expression on the recurrence-free period. However, no marker combination was able to outperform the prognostic value of S100A5 (data not shown), except if the patients’ ages were considered (see below).

### Prognostic value for S100A5 in relation to other factors

Cox regression analyses were carried out to determine the relationship between the recurrence periods and the different factors suspected of yielding prognostic values. We thus considered S100A5 SI, the patients’ ages, sexes and their tumour sites. Indeed, the patients who experienced a recurrence (constituting the ‘YES’ group in Figure 4a) were significantly younger than the patients followed up for at least 7 years without any recurrence (the ‘NO’ group in Figure 4a). As reported in Table 1, 13 of the 14 recurrent cases involved female patients, while the sex distribution was almost even in the non-recurrent group. Concerning the tumour sites, we observed that the patients with meningiomas in the convexity or the falx were associated with better remission rates than those
Recurrence in WHO grade I meningiomas

with parasagittal meningiomas or meningiomas at the base ($P = 0.01$, data not shown). Table 2 summarizes the best models generated on the basis of the four factors considered. Table 2 indicates the overall significance of each model, the list of the variables considered, their respective coefficients in the models (with their exponential forms) and the corresponding $P$-values evaluating the significance of the predictive contribution of the variables to the overall model. In fact, of the four factors analysed, the patients’ sexes and tumour sites did not contribute any significant independent information (Table 2). Furthermore, the best model for predicting the recurrence period was obtained by combining the S100A5 SI and the patients’ ages, both of which contributed significant independent information (Table 2). In contrast, the S100A5 LI was related to the patients’ ages, as shown in Figure 4(b). Figure 4(e) confirms that this was not the case for the S100A5 SI. Lastly, we tried to establish a threshold value (by means of a decision-tree technique) for the patients’ ages in order to distinguish as efficiently as possible between the recurring and the non-recurring meningiomas. The best threshold so established was 55 years (data not shown). While the two groups of patients so determined exhibited few differences in terms of recurrence (Figure 4d), Figure 4(e) suggests that their ages seemed to be an additional factor of recurrence (in comparison to the groups established in Figure 3b). This has, of course, to be confirmed on a larger series of patients.

Discussion

Predicting recurrence in meningiomas is still a real challenge. The two generally accepted predictive factors are

Figure 2. Morphological illustrations ($×400$) of the expression of S100A5 in grade I meningiomas. While (A) shows a very weak staining (rather nonspecific) observed in a recurrence case, (B) illustrates the moderate staining observed in a non-recurrence case.

Figure 3. The remission curves (expressed in years) for the two groups of patients determined in Figure 1 on the basis of the S100A5 labelling index (LI) (a) and the S100A5 staining intensity (SI) (b). The patients with tumour recurrences are indicated by dots and those without by crosses (+). The $P$-values were computed by means of Gehan’s generalized Wilcoxon test. The arrows in the two frames indicate the cases of recurrence (in the curve for the group of patients with a lower recurrence risk) occurring fewer than 10 years after surgery.

Histopathological grading and the quality of surgical resection [1,3,7–10]. It is well established that WHO grade II and III meningiomas recur more often than WHO grade I meningiomas [1–3,9], and that within grade I histological subtyping does not contribute any predictive value with respect to recurrence [2]. The quality of surgical resection (Simpson grading scale) is the second accepted factor predictive of recurrence [1,2,8,9]. The recurrence rate is higher in the case of partly resected (i.e. Simpson 3, 4 or 5) meningiomas than in the case of totally resected ones (i.e. Simpson 1 or 2). Both the recurrence-free and the survival periods (after surgical resection) are longer if the resection is complete [6,10]. However, different types of clinical behaviour may be encountered in a homogeneous group of meningiomas with the same histological grade and the same degree of resection, as some tumours can recur without explanation while the others do not. For example, Philippon and Cornu [1] described a recurrence rate of 5% in the case of totally resected (Simpson 1 or 2) meningiomas situated in the convexity.

Figure 4. The influence of the patients’ ages on tumour recurrence. (a) characterizes the distribution of the patients’ ages (median, 25% and 75% percentiles) according to their recurrence status. Similarly, (b) and (c) illustrate the distribution of the patients’ ages according to the S100A5 labelling index (LI) and the S100A5 staining intensity (SI), respectively. The P-values indicated in (a–c) were computed by means of Mann–Whitney tests (N.S., not significant). (d) shows the remission curves associated with patients younger or older than 55. (e) illustrates the remission curves obtained after combining the patients’ ages (illustrated in d) and the S100A5 SI (illustrated in Figure 3B). In (de) the patients with tumour recurrences are indicated by dots and those without by crosses (+). The P-values were computed by means of Gehan’s generalized Wilcoxon test.

Table 2. Cox regression models

<table>
<thead>
<tr>
<th>Model/P-value</th>
<th>Variable</th>
<th>β</th>
<th>exp(β)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100A5, patients’ ages, sexes and tumour sites</td>
<td>S100A5_SI</td>
<td>-2.52</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.04</td>
<td>0.96</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>-0.12</td>
<td>0.89</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Site</td>
<td>-0.68</td>
<td>0.51</td>
<td>0.25</td>
</tr>
<tr>
<td>S100A5, patients’ ages and tumour sites</td>
<td>S100A5_SI</td>
<td>-2.55</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.04</td>
<td>0.96</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Site</td>
<td>-0.70</td>
<td>0.49</td>
<td>0.20</td>
</tr>
<tr>
<td>S100A5 and patients’ ages</td>
<td>S100A5_SI</td>
<td>-2.74</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.05</td>
<td>0.95</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The ‘Model/P-value’ corresponds to the overall significance of the models. The equation at the basis of the Cox regression model is an exponential function of a linear combination of the variables considered, where β represents the coefficient of each variable and exp(β) its exponential value. The P-value represents the level of significance of each variable contribution to the model (leading to the conclusion that β is significantly different from zero if P < 0.05). SI, staining intensity.

gliomas recur within a few months of initial surgery, others do not recur before a number of years have elapsed. The different clinical factors used as a standard procedure to predict recurrence cannot explain these variations [2]. This is why some authors have made use of CT scans to investigate other factors seen as being complementary to the process of predicting the aggressive behaviour of WHO grade I meningiomas. These radiological factors include, for example, the growth rate and the time required for tumour volume doubling, the tumour shape and the presence of an oedema around the meningioma [2,6,11]. The variations observed in tumour volume doubling could explain why some studies report a statistically significant relationship between cell kinetics and recurrence [14,16]. However, others fail to obtain any such significant relationship [12,13,15]. It is thus interesting to investigate other types of biological factors such as those involved in cell–cell interaction or invasion. We decided to analyse and compare galectins, cathepsins and S100 proteins because of their involvement in the development of brain tumours and the progression of their malignancy. Our results demonstrate that only the determination of the immunohistochemical expression of S100A5 is able to identify meningioma recurrence. While S100A5 is expressed in very restricted regions of the adult brain [44], it is over-expressed in astrocytic tumours and shows no change in expression across the four WHO histopathological grades [28]. In contrast, significant variations were observed across different clinical groups set up on the basis of tumour aggressiveness (with significantly different clinical outcomes) [29]. In this case, the level of S100A5 expression increases in accordance with tumour aggressiveness. In the present study, we show an inverse relation between the level of S100A5 expression and the risk of recurrence of WHO grade I meningiomas.

The influence on meningioma recurrence of patients’ ages remains controversial. Some authors [1,2] show a higher frequency of recurrence in patients younger than 40 years. Others [3] have found nothing significant in the age on recurrence. However, our data suggest that patients’ ages could be involved in the risk of meningioma recurrence (Figure 4a). By combining our patients’ ages and the intensity of the S100A5 immunostaining, we identified a group of cases associated with a particularly high risk of recurrence (about 90% 10 years after surgery); this group consisted of young patients with meningiomas expressing a low level of S100A5 immunostaining intensity (Figure 4e). These results naturally have to be validated on a larger series of meningiomas characterized by the same clinical and biological features as those investigated here.

In conclusion, the present study suggests that S100A5 could play a role in the recurrence of totally resected WHO grade I meningiomas. This S100 protein could thus be used as a prognostic marker to identify patients who require a more intensive follow-up after the total resection of a benign meningioma.

Acknowledgements

This work has been carried out on the basis of grants awarded by the Fonds de la Recherche Scientifique Médicale (FRSM, Belgium), the Y. Boël Foundation (Brussels, Belgium), the Dr.-Mildred-Scheel-Stiftung für Krebsforschung and the Swiss National Science Foundation (31–61821.00).

R. Kiss is a Director of Research and C. Decaestecker a Senior Research Associate with the Belgian National Fund of Research (F.N.R.S., Brussels, Belgium).

References


Recurrence in WHO grade I meningiomas


Received 1 May 2003
Accepted after revision 8 September 2003