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Relationship Between S100 Protein Expression and Grading Meningioma

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Abstract: Meningioma is the most common type of benign brain tumor in adults and mostly originates from the meningeal layer of the brain and spinal cord. The prevalence of meningioma in the world is estimated to be about 24-30% of intracranial primary brain tumors. This tumor is classified into three groups based on grade, grade I (benign), grade II (atypical), and grade III (anaplastic). The S100 protein is not specific to meningiomas but some studies have shown that the expression of S100 protein is stronger in grade I meningiomas than in grade II and III meningiomas. Based on these findings, the authors are interested in analyzing whether there is a relationship between S100 expression and meningioma grading. The determination of S100 protein expression is very necessary as a reference in determining the prognosis and selection of the best therapy for patients. This research was carried out in the period from January 2021 to December 2021. 9 samples were included in this study according to the inclusion and exclusion criteria. The data was analyzed using SPSS version 26. The results of this study: A normality test was carried out with the Shapiro Wilk test and a value of p=0.34 (CI 95%) was obtained using Spearman analysis.

Keywords: Grading; Meningioma; S100 protein

Introduction

Meningioma is the most common type of benign brain tumor in adults and mostly originates from the meningeal layer of the brain and spinal cord (Putri et al., 2023; Bassiouny et al., 2012). Meningiomas account for 36.60% of overall primary brain tumors and 53.20% of benign primary brain tumors. The prevalence of meningioma in the world is estimated to be about 24-30% of intracranial primary brain tumors (Maggio et al., 2021; Ogasawara et al., 2021; Mizrachi et al., 2024). The incidence rate of meningioma in the United States ranges from 97.50 per 100.000 population with more than 170.000 individuals already diagnosed with meningioma (Kalamarides & Peyre, 2020). The World Health Organization (WHO) 2021, classifies meningioma into three groups based on grade, grade I (benign), grade II (atypical), and grade III (anaplastic) (Louis et al., 2021). Grade I (benign) meningioma has a slow growth rate based on imaging, morphology, and patient prognosis studies, grade II (atypical) meningioma is characterized by an increase in mitosis activity to 4-19 mitosis/hpf, invasion of the brain's parenchymal tissue, spontaneous necrosis, and increased cellularity while grade meningioma III (anaplastic) is characterized by a progressive increase in mitotic activity reaching 20 mitoses/hpf as seen in the histopathological picture (Meuten et al., 2021).

The difference in histopathological picture of each grading meningioma makes it a marker to make it easier

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for a pathologist to determine the grading of meningioma (Behling et al., 2021; Li et al., 2019; Ammendola et al., 2021). Determination of meningioma grading can not only be done through histopathological examination but can also be done by examination of antibody markers (Sobhy et al., 2011; Huntoon et al., 2020). Examination of S100 expression in meningiomas has not been done much because it is considered non-specific to meninge cells (Azamat et al., 2024; Ülgen et al., 2019). Initially, the expression of S100 protein was believed to be limited to glial cells and the central nervous system (CNS) but several studies have shown the distribution of S100 protein outside the CNS (Sheloukhova & Watanabe, 2024), namely in stellata cells from the adenopituitary, ganglion cells, adrenal medulla, melanocyte cells, chondrocyte cells, and schwannoma. The S100 protein is not specific to meningiomas but some studies have shown that the expression of S100 protein is stronger in grade I meningioma than in grade II and III meningioma (Liu et al., 2018; Poulen et al., 2020; Sefo et al., 2024). The American Academy of Cerebral Palsy defines it as abnormal movement or motor function changes caused by accidents, injuries, and diseases of the nervous system abnormality (Zhou et al., 2017).

Based on these findings, the authors are interested in analyzing whether there is a relationship between S100 expression and meningioma grading. The determination of S100 protein expression is very necessary as a reference in determining the prognosis and selection of the best therapy for patient's cytomegalovirus, herpes simplex), drugs, abortion attempts, smoking, and alcohol consumptions. Perinatal risk factors are birth trauma, prematurity, and low birth weight. Postnatal risk factors are cerebral hemorrhage, infections such as meningitis and encephalitis that occur in the first 6 months of life, and carbon monoxide or heavy metal contamination.

Method

Research Design

This study is an analytical observational study with a cross-sectional analytical study approach to determine the expression of S100 on meningioma grading.

Population, Research Samples, Sampling Techniques

The study population is all paraffin blocks of grade I, II, and III meningioma patients for the period January 2021 to December 2021. The criteria for patient inclusion are derived from tumor tissue obtained from surgical preparations, and derived from meningioma tumor tissue whose grading has been determined by an anatomical pathologist. While the exclusion criteria are that there is a diagnosis of other malignancies other than malignancy in the preparation, paraffin blocks are not representative and damaged, tumor tissue is too small or few. The calculation of the research sample used Fisher's formula and obtained as many as 9 samples. The research samples were then analyzed using the immunohistochemical (IHC) method in the anatomical pathology laboratory.

Statistical Analysis

Data obtained were processed using the Statistical Package for the Social Science (SPSS) version 26.0 program. Numeric data is presented as descriptive data without any statistical test. The data normality test was carried out using the Shapiro wilk method, and the correlation analysis was carried out using the Spearman correlation test.

Results and Discussion

Results

S100 immunohistochemistry examination carried out on 9 tissue samples of meningioma patients obtained positive results in 2 samples, namely grade 2 meningioma and grade 3 meningioma (10% and 40%, respectively), while the other 7 samples were negative. Assessment of S100 protein expression by calculating the percentage of positive tumor cells (brown) in the cytoplasm of tumor cells using a binocular light microscope at 100x magnification. The expression of the S100 protein in each of the meningioma grades is presented in table 1.

Table 1. Expression of S100 Protein in Grade 1, 2, and 3 Meningiomas

Sample Number	Grade	S100 (%)
949/22	1	0
999/22	1	0
631/22	1	0
1255/21	2	0
333/21	2	10
69/22	2	0
1798/21	3	40
2387/21	3	0
1241/22	3	0

The data obtained from this study was tested for normality with the Shapiro wilk test, non-homogeneous and non-normally distributed data ($p < 0.05$). The correlation between S100 expression and meningioma grading was tested using the Spearman correlation test. The results of the analysis showed that there was no correlation with the value of the Spearman correlation coefficient (rs) with p=0.34. The absence of correlation of S100 expression with meningioma grading is presented in the form of scattered plots in Figure 1.

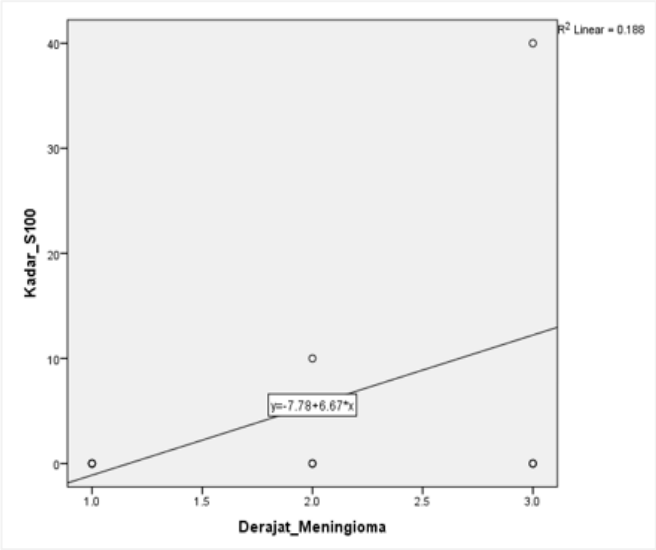

Figure 1. The form of scattered plots

In this study, the S100 protein was not expressed in grade 1 meningiomas characterized by the non-digestion of all parts of tumor cells while in grade 2 and grade 3 meningiomas only partially dissolved in tumor cells, namely 10% and 40% of the total tumor cells observed at 100x magnification. A comparative image of S100 expression in meningiomas is presented in figure 2.

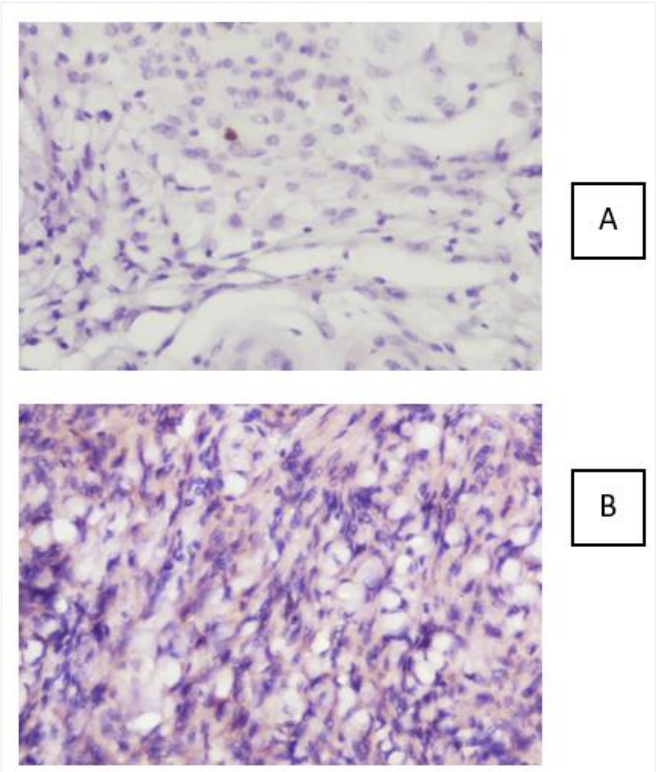

Figure 2. S100 protein expression in meningioma, 100x magnification (A. S100 protein is not expressed in meningioma; B. Protein S100 is expressed in meningioma)

Discussion

Specific markers that can be used as definite prognostic marks for brain tumor patients, meningioma is not yet clearly known (Franca et al., 2023; Behling, Hempel, et al., 2021; Halabi et al., 2023). Most meningioma patients can be completely cured if the tumor can be removed completely, although recurrence is still reported in some cases. In one study that observed meningioma patients for 25 years, almost 40% of meningioma patients who had undergone surgery experienced a recurrence. The high recurrence rate of meningioma patients is one of the reasons for the need to identify meningioma tumors that have the possibility of recurrence or become aggressive from the early phase (Brastianos et al., 2019; Zuo et al., 2019). The existence of specific markers, both immunohistochemically and serologically, will greatly help diagnose the early phase of meningioma. An increase in serum S100 levels can be used to identify meningiomas that have the potential to become aggressive. Immunohistochemical examination with S100 review has been widely used in the diagnosis of tumors originating from nerve fibers, S100 can be used as one of the main biomarkers as a determinant of grading meningioma (Yuen et al., 2025; Aung et al., 2024).

In this study, the S100 protein was expressed positively in 2 tumor cell samples and negatively in 7 tumor cell samples. S100 protein was extracted 0% in all grade 1 meningioma samples, 10% extracted in 1 grade 2 meningioma tumor sample, and 40% extracted in 1 grade 3 meningioma sample. This result is in line with a study conducted by Behling et al, where of the 1669 samples examined most of the samples did not express the S100 protein, 211 samples were positive and the rest were negative. The study by Boulagnon et al showed a similar point where the S100 protein was positively expressed in only a small percentage of tumor cells, with an average of 5% (Sinha et al., 2008; Iwadate et al., 2015; Raso et al., 2024). This result may be due to the fact that most of the S100 protein will be bind to proteins that are important components of the epidermal differentiation complex that correlate with tumor differentiation. Meningiomas are benign tumors that tend to be unwidely differentiated so most of the S100 protein will not be expressed in meningiomas.

The unexpressed meningioma in most samples was associated with a lower potential for recurrence compared to those that were positively suppressed (Trivedi et al., 2024; Silva et al., 2025), conducted by Prihartomo et al, found that the S100 protein was most expressed in grade 1 meningioma, followed by grade 2 meningioma, and least in grade 3 meningioma (Nassiri et al., 2021). Dunn et al. (2019), obtained higher expression of S100 in grade 1 meningioma compared to grade 2 or 3 meningioma. This result is different from

this study where the S100 protein is more expressed in grade 2 and 3 meningiomas. This result is due to the fact that the expression of S100 in certain tissues reacts differently to tumor differentiation, for example, the decreased S100A2 protein is associated with tumor differentiation of laryngeal squamous cells. Decreased expression of S100A8/S100A9 in the esophagus correlated with poor differentiation of tumor cells conversely, increased expression of S100A8/S100A9 correlated with poor differentiation in breast carcinoma (Wang et al., 2018; Zhang et al., 2017). The data showed that high and low expression of S100 protein was strongly related to tumor differentiation (Sinha et al., 2008; Riehl et al., 2009). The same research model was conducted on NSCLC lung carcinoma where positive expression of S100 was associated with a better prognosis (Lee, 2009; Allgöwer et al., 2020).

Conclusion

This study shows that S100 protein expression has no significant correlation with histopathological grading of meningioma, contrary to previous assumptions. Nevertheless, S100 still shows promising potential as a prognostic marker to predict clinical outcomes in meningioma patients.

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Conflicts of Interest
The authors declare no conflict of interest.

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