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Relationship of P53 Protein With Histopathology Degree of Intracranial Astrocytoma at Haji Adam Malik Hospital Medan

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Abstract : One of the prognosis factor of patients with astrocytoma is a proliferation index. Sometimes it is difficultin determine whether it is an astrocytoma astrocytoma grade 2 or level 3. The p53 protein is involved in a variety of malignancies including brain tumors. P53 genetic changes commonly occur in this astrocytoma. This is a cross sectional analytic study aimed to look at the relationship between the degree of histopathologic WHO p53 in patients with intracranial astrocytomas in HAM Hospital. The results of this study found a significant relationship between expression of p53 on astrocytomas histopatologi (p = 0.002).
Keywords : Astrocytoma, astrocytoma degrees, p53.

Introduction

Glioma is the most common primary tumor that is half of all primary brain tumors. Glioma is a neuroectodermal tumor derived from sustentakular neuroglia cells[1,2]

The consistent genetic changes that can always be found in patients with astrocytoma are mutations of the p53 gene on chromosome 17 at 17p53. This gene has an important role in the apoptotic function and cell cycle regulation, the disruption in the function of this gene results in accelerated growth and malignant differentiation from astrocytes.[1,2]

Astrocytoma is divided into 4 degrees in the WHO classification. It is important to be able to distinguish second degree astrocytoma and third degrees as this greatly differentiates the management and prognosis of the patient.[3]

p53 protein is a tumor suppressor gene (TSG) found on chromosome 17p, which has an integral role in a number of cellular cellular processes including cell cycle, apoptosis, angiogenesis and cell differentiation. P53 is involved in various malignations including brain tumors. Genetic changes in p53 are common in astroliomas.[4]

A study correlating p53 with astrocytoma degree in Indonesia has never been done so it is not yet known whether the role of p53 which previous studies have shown helpful in determining the degree of astrocytoma can also be used in populations in Indonesia. Therefore, researchers interested to examine the relationship between p53 with astrocytoma classification according to WHO.

Methods

This is a cross sectional analytic study which analyze the correlation between proliferation rate of p53 and degree of astroctoma patient of RSUP HAM on October 2015 - October 2016. The research population is

astrocytoma patient. In that period, there were 25 samples of astrocytoma. The inclusion criteria were patients who had been clinically diagnosed with intracranial astrocytoma, a patient who had performed head MRI with intravenous gadolinium contrast, the patient had surgery so that there was a tissue tumor that could be confirmed as astrocytoma by the Anatomy Pathology division and the diagnosis was confirmed by Anatomical Pathology examination. Exclusion criteria are accompanied by other systemic diseases such as diabetes mellitus, kidney and liver disease, recurrent occurrence or recurrence and other tumors in the body. The rate of p53 proliferation is assessed by immunohistochemical staining. All specimens of astrocytoma paraffin blocks that had previously been subjected to hematoxylin-eosin base staining and confirmed as an astrocytoma from October 2015 to October 2016 were collected and recorded patient data obtained from the patient's medical record and an assessment of the neurosurgery department of the RSUP. HAM Medan. Medical and demographic data of name, sex, age, degree of astrocytoma based on WHO, Anatomy Pathology number, and outcome were computerized by Chi square statistic test. A P value of 0.05 is considered to be a significant relationship. While the value of P> 0.05 is considered there is no significant relationship.

Result

In this study we found that the characteristics of astrocytoma patients based on gender are women as many as 10 people (40%) and men 15 people (60%). Male predominates female with a ratio of 1.5: 1. (Table 1). The age group shows that the highest number of astrocytoma occur in age group 40-49 years that is equal to 8 cases (32%) with the frequency of occurrence is least found in the age group 0-9 years and 60-69 years ie 1 case. (4%) (Table 2).

Table 1. Distribution based on Sex

Sex	**N**	**%**
Male	15	60
Female	10	40
Total	25	100.0

Table 2. Descriptive Analysis Based on Ages

Ages Group	**N**	**%**	**Mean**	**Median**	**Std. deviasi**	**Min**	**Max**
0 – 9	1	4,0	35,9	37,0	14,6	9	68
10 – 19	3	12,0					
20 – 29	4	16,0					
30 – 39	5	20,0					
40 – 49	8	32.0					
50 – 59	3	12,0					
60 – 69	1	4,0					
Total	25	100.0					

Table 3. Distribution of Astrocytoma Grade in This Study

WHO Grading	**N**	**%**
Grade I	9	36,0
Grade II	7	28,0
Grade III	4	16,0
Grade IV	5	20,0
Total	25	100.0

Table 4. Distribution of P53 Based on Astrocytoma Classification

P53	Astrocytoma Grade I	Astrocytoma Grade II	Astrocytoma Grade III	Astrocytoma Grade IV	p
Negative	3 (33,3%)	0 (0,0%)	0(0,0%)	0 (0,0%)	
Positive 1 (≤ 5% nukleus)	6(66,6%)	3 (42,8%)	0 (0,0%)	0 (0,0%)	0,001*
Positive 2 (5-30% nukleus)	0(0,0%)	4(57,1%)	3(100%)	2(33,3%)	
Positive 3 (>30% nukleus)	0(0,0%)	0(0,0%)	0(0,0%)	4(66,6%)	
Total	9 (100%)	7 (100%)	3 (100%)	6 (100%)	

**Spearman*

This study divided the classification of astrocytoma based on WHO degree shows that the most frequent are first degree astrocytoma with the number of 9 patient (36,0%) cases. Then followed by 7 cases of second astrocytoma (28,0%), third degree as many as 4 cases (16,0%) and fourth degree astrocytoma counted 5 cases (20,0%). (Table 3) The number of mitoses measured by the astrocytoma classification found that the majority of first degree astrocytomas have a weak mitosis of 9 samples. Second degree astrocytoma had weak mitosis of 3 samples (42.8%) and strong mitosis of 4 samples (57.1%). Astrocytoma third degree has a strong mitosis of 3 samples (100%) and fourth degree astrocytoma has a strong mitosis of 6 samples (Table 4). Based on the results of p53 staining with astrocytic outcome, 16 surviving patients (64%) and 9 patients died (36%), while patients with severe p53 staining were 7 live patients and 6 patients who died (Table 5). In grade I astrocytoma, there were 6 living patients (66.6%) and 3 patients who died (33.3%). Grade II astrocytoma there were 6 living patients (85,7%) and 1 patient died (28%), third degree there were 3 living patients (75%) and 1 patient died (25%) and fourth degree there was 1 patient who lived (20%) and 4 patients died (80%) (Table 6).

Table 5. Distribution of P53 based on Outcome

P53	Live	Die	Total	p
Negative	1 (33,3%)	2 (66,6%)	3 (12%)	0,097
Positive 1	8 (88,8%)	1 (11,1%)	9 (36%)	
Positive 2 Positive 3	6(66,6%) 1(25%)	3(33,3%) 3(75%)	9 (36%) 4(16%)	
Total	16 (64%)	9 (36%)	25 (100%)	

Chi square

Table 6. Distribution of Astrocytoma Classification and Outcome

WHO Grading	Live	Die	Total	p
Grade I	6 (66,6%)	3 (33,3%)	9 (36%)	0,118
Grade II	6 (85,7%)	1 (14,2%)	7 (28%)	
Grade III	3 (75%)	1(25%)	4 (16%)	
Grade IV	1(20%)	4(80%)	5 (20%)	
Total	16 (64%)	9 (36%)	25 (100%)	

Chi square

Discussion

Astrocytoma is the most common type of glioma tumor that is> 75% of all gliomas. Glioma itself is a neuroectodermal tumor derived from a sustentacular neuroglia cell.[11] Astrocytoma is classified into 4 degrees

where degree I and degree II are classified as low grade astrocytoma, whereas degrees III and degree IV are classified into high grade glioma.[1,2]

The p53 gene is a gene suppressor tumor (TSG) found on the 17p chromosome, has an integral role in a number of cellular processes, including cell cycle, apoptosis, angiogenesis and cell differentiation. P53 is involved in several varieties of malignancy including in brain tumors. The genentic change in p53 is common in astroglioma. Changes were studied about 1-3 grades of 3 grades in adult astrocytoma.

High-grade astrocytomas can be found at any age and are more commonly found in men than women with a ratio of 1.5: 1. In anaplastic astrocytoma, the average age at diagnosis is about 40 years. For glioblastoma, the mean age at presentation was 62 years. Even with optimal therapy, the average survival rate is less than 2 years in glioblastoma and between 2 to 5 years in gliosarcoma.[1,6] In this study, we obtained 25 samples of intracranial astrocytoma patients who went to RSUP. HAM Medan. 10 female samples and 15 male samples were obtained. With the ratio of men and women is equal to 1.5: 1.

In 2014 Thotakura through his study explained the same thing that the incidence of astrocytoma is more common in male than in females with male proportions: women = 1.84: 1.5,[11] This supports the previous literature that astrocytomas found mostly in male rather than in females. High grade astrocytoma in women is more common in menopausal age so there is speculation that female hormones have a protective effect on astrocytoma.[1]

Most Astrocytoma patients is in the range 40-49 years old (32%) with median of 37, the youngest age is 9 years and the oldest age is 68 years. Previously Thotakura, 2014 suggests a similar thing where in the study found that the highest number of astrocytoma occur in the fourth and fifth decade that includes 49.52 of the entire sample.[5,11]

In this study we found that astrocytoma degree I based on WHO classification is the most common type of astrocytoma that is equal to 36%, followed by degree II and degree IV respectively by 24%, and degree III with 14%. This result does not resemble previous study where the highest incidence was found in second degree astrocytoma with 39,9% followed by fourth degree astrocytoma which was 36,2%, degree III astrocytoma 14,3% and astrocytoma degree I which equals to 9,5% .[5]

Many studies have shown changes in p53 immunoexpression in astrocytic tumors, generally related to secondary glioblastoma rather than the primary. This change is considered a significant predictor of prognosis in some cancers in humans and is sometimes considered to predict a response to chemotherapy. In a meta-analysis study conducted by Levidou, et al in 2009 involving 14 studies from 1992 to 2006, it was concluded that p53 changes in astrocytoma were poor predictors of mortality.[7,8,9] Similar to this study, it was found that no significance between expression of p53 on patient mortality (p 0.097). However, unlike the studies conducted by Pollack, et al and Sherwin, et al which found that there is a relationship between p53 expression in astroglioma with higher degrees and with poor prognosis and poor outcomes. There was a significant increase in p53 in GBM (p 0.0001) .[8,10]

Khattab et al stated that there is a relationship between p53 gene expression and histopathologic classification of astrocytoma (p 0.0001) .[12] This is similar to what we found in this study where there was a significant relationship between p53 expression of histopathologic classification of astrocytoma (p 0.002). Previous reports such as those in Khattab explained that histopathologic features and clinical prognosis factors (age, sex, extent of resection, and tumor location) were independent parameters and had no association with p53.[13]

To see if the WHO classification had a role in the prognosis in this study, Chi-square test was performed with $p = 0.001$ ($p < 0.05$). This suggests that there is a significant relationship between the WHO classification and the prognosis of the patient.

Conclusion

The conclusion of this study is that there is a significant relationship between p53 classification of astrocytoma histopathology, there is no significant relationship between p53 with outcome and there is no

relation between WHO astrocytoma classification with outcome. Examination of p53 as investigation in assisting in diagnosis of astrocytoma.

Several suggestions for further research is the need to do research with a larger sample size. In conducting further research, it should be considered other causes of mortality such as surgical complications and secondary infections. Other factors such as radiotherapy and chemotherapy in high grade astrocytes should also be taken into account in determining outcomes.

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