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Original Article

Orbital Meningioma in Patients with Hormonal Contraceptive History: Investigating The Role of mTOR and PTEN

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ABSTRACT

Introduction and Objective: Meningiomas are among the most common low-grade intracranial tumors that can spread to the orbital cavity. Long-term use of hormonal contraceptives has been suggested to play a role in the development of meningiomas. Increasing levels of the mammalian target of rapamycin (mTOR) are considered to promote cell proliferation and prevent apoptosis. Mutations in the phosphatase and tensin homolog (PTEN) gene may increase neoplasm severity. This study aims to determine the role of mTOR and PTEN in meningioma tissues. Method: This cross-sectional study included 21 patients with meningiomas confirmed by histopathological examination. Interviews were conducted to assess their background knowledge of obstetrics, gynecology, and contraceptive use. Expression of mTOR and PTEN was assessed by real-time PCR. Result: The average age in this study was 44.93 years (SD±6.69). We also found that the average age of first-time use of contraception was 24.00 years old (SD±5.01), while the average duration of contraceptive usage was 197.31 months (SD±73.55). Among 16 patients, all subjects showed an increased expression of mTOR and PTEN. Quantitatively, there was an increase in mTOR (27,9 + 16,5) and PTEN (5.9 + 3.2) expression in tumor tissue.
Conclusion: There was a significant increase in mTOR and PTEN expression in tumor tissue. Thus, mTOR and PTEN may play an important role in meningioma development.

Introduction

Meningioma is the commonest primary central nervous system tumor, accounting for about 37.6% of them, and approximately 50% of all benign brain tumors.[1] Few studies have examined the risk factors associated with a diagnosis of meningioma, with two categories of exposure, hormones (both endogenous

and exogenous) and radiation, most strongly associated with meningioma risk. Epidemiologic studies find that the association between hormonal and reproductive factors and the risk of brain tumors is conflicting. Female meningioma-related conditions include breast cancer, uterine fibroid tumors, and endometriosis.[2,8]

Phosphatase and tensin homolog on chromosome 10 (PTEN) is one of the most frequently inactivated tumor suppressors in human cancer, due to genetic alterations or transcriptional/post-transcriptional inhibition; moreover, even a partial loss of its function (haploinsufficiency) may cause neoplastic transformation. 3 mTOR protein kinase nucleates a major eukaryotic signaling network that coordinates cell growth with environmental conditions and plays a fundamental role in cell and organismal physiology. Deregulated mTOR signaling is implicated in the progression of cancer and diabetes, as well as the aging process. Many aspects of mTOR function and regulation have only recently been elucidated, and many more questions remain unanswered.[4] This study aims to determine the role of mTOR and PTEN in meningioma tissues.

Method

This is an observational study with a cross-sectional design. The samples were obtained from the medical records of 21 patients with orbitocranial meningioma who underwent orbitotomy at Dr. Sardjito General Hospital, Yogyakarta, from 2010 to 2016. Histopathological examination was performed to confirm the diagnosis.

The study's inclusion criteria were women who had used progesterone as a hormonal contraceptive in the past, a head CT scan that revealed an orbitocranial meningioma, and an anatomical pathology investigation that revealed a meningioma tumor coming from the meninges tissue.

The protocol for this study was approved by the Ethical Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, and was conducted in accordance with the ethical tenets of the Declaration of Helsinki.

Real-time polymerase chain reaction (RT-PCR) was used to analyze the mRNA expression of mTOR, PTEN, and PR in meningioma tissue. All treatments are performed by qualified professionals who seasoned experts directly oversee. Venous blood is drawn from the brachial vein and placed in an EDTA tube. Paraffin blocks of meningioma tissue were cut to a thickness of 4 µm. Total RNA was extracted from blood and meningioma tissue using the Geneaid Blood/Cell Total RNA Mini Kit (Geneaid Biotech, Taiwan). Then, the total RNA underwent reverse transcription, followed by RT-PCR analysis in 48-well plates using the KAPA SYBR FAST One-Step Universal Kit (Sigma-Aldrich, St. Louis, MO, USA) and the DTlite RT-PCR System (DNA–Technology, Russia). The amplification results were analyzed using the DTlite Real-Time PCR System Software (DNA–Technology) and normalized to GAPDH mRNA levels.

All data were identified and analyzed using SPSS Statistics, with descriptive and frequency functions employed.

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Results and Discussion

The data was taken from medical records from 2010 – 2016; from this period, 21 patients were obtained with a history of using hormonal contraceptives, and 5 subjects were excluded. Table 1 shows the characteristics of the subjects, including age distribution, age at first use of hormonal contraception, and length of hormonal contraceptive use.

Table 1. Characteristic of Subject

Age	Frequency	Percentage	Mean	Median
20-30	1	6.25%		
30-40	1	6.25%	44.938 + 6.69	46.5
40-50	12	75%		
50-60	2	12.5%		
Total	16	100%		

From the table 1, the subject's average age was 44.938 ± 6.69 years, the average age at first use of a hormonal contraceptive was 24 ± 5 years, the most common age group in the sample was 40-50 years old, and the average length of hormonal contraceptive use was 197 ± 73 months.

Table 2. First usage of hormonal therapy

Age	Freq	Percentage	Mean	Median
< 20	2	12.50%		
20-25	9	56.25%		
25-30	3	18.75%	24 + 5	22
30-35	2	12.50%		
Total	16	100%		

Table 3. Duration of hormonal contraceptive

Month	Freq	Percentage	Mean	Median
<100	2	12.50%		
100-200	7	43.75%	197.31	180
200-300	7	43.75%		
Total	16	100.00%		

The minimum length of contraceptive usage was 84 months, and the maximum usage of hormonal contraceptives was 300 months, or equal to 25 years. The expression of average mTOR was 27.9 + 16.5, with the highest level being 68.59, and the lowest level being 9.38. while the average PTEN expression was 5.9 ± 3, and the highest PTEN level was 13.92.

Table 4. Frequencies of the mTOR level.

mTOR Level	Freq	Min	Max	Mean
<10	1			
10-20	4			
20-30	5			
30-40	4	9.38	68.59	27.9 + 16.5
40-50	-			
>50	2			
Total	16			

Table 5. Frequencies of PTEN level.

PTEN Level	Freq	Min	Max	Mean
<5	9			
5-10	5	2.1	13.9	5.9 +
10-15	2	4	2	3.2
Total	16			

The table shows that the expression of mTOR and PTEN was increased in some patients with meningioma tissue.

Discussion

The average subject age was 44 years, and in the age range 40-50, we could see the highest incidence rate of meningioma. According to a previous study, Wiemel et al. (2010) found that the highest incidence rate of meningioma occurs at age 40, with a second peak at age 85. The longest usage of a hormonal contraceptive was 25 years. The incidence of meningioma increased with the use of hormonal therapy, with a minimum of at least 10 years, resulting in an odds ratio of 2.7.[5]

Under normal conditions, mTOR is a major regulator of cell growth and division. However, in tumor cells, abnormal mTOR signaling promotes significant growth, and tumors can ultimately metastasize and invade healthy cells. The PI3K/Phosphate and fungi homology deleted on chromosome 10 (PTEN)/AKT/TSC pathway is the main activator of mTOR1, and mutations in this pathway lead to malignant tumors. PTEN expression is often silenced by epigenetic, genetic, and post-transcriptional mechanisms, thereby upregulating the mTOR pathway in most malignant tumors.[6,7]

In this study, the levels of mTOR and PTEN were increased in tumor cells, with mean values of 27,9 ± 16,5 for mTOR and 5.9 ± 3.2 for PTEN across varying durations of hormonal therapy. In this study, increased PTEN expression in meningioma tissue was associated with low-grade meningiomas or meningiomas with a low recurrence rate. In another study, Junpeng et al. (2019) found that PTEN expression declined in high-grade meningioma and concluded that low PTEN expression can predict recurrence rate and mortality in meningioma.[8] The exact role that the protein PTEN plays in these higher-grade tumors is still poorly understood and may be related to the function of PTEN in the nucleus.[9] A limitation of this study is that the samples were not classified by WHO grade, and the relationship between PTEN and mTOR levels in tissues from meningiomas of varying grades could not be assessed.

Conclusion

This study demonstrates that mTOR and PTEN expression are increased in orbital meningioma tissues in patients with a history of long-term hormonal contraceptive use. These findings suggest that both pathways may play an important role in the development and progression of meningioma.

Declarations

Statement on the Use of Artificial Intelligence

AI was used to assist in drafting the declarations section.

Author contribution statement

Yunefesta Respati Angka contributed to manuscript preparation and revision, data collection, and data analysis. Datu Respatika contributed to manuscript revision, data collection and analysis, and final approval of the article.

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Conflict of interest

The authors declare no conflicts of interest regarding the publication of this article.

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