Characteristics and Correlation Between Progesterone Receptors and The Use of Hormonal Contraceptive in Women with Meningioma in dr. Cipto Mangunkusumo National General Hospital

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Abstract
Meningiomas are the most common primary, intracranial and extra axial tumours, estimated for 30% of all intracranial tumors. The use of hormonal contraceptive is one of the risk factors for meningioma, but the studies still have controversial results. The purpose of this study is to describe the characteristics and to correlate between progesterone receptor and the use of hormonal contraceptive in women diagnosed with brain tumor meningioma. This is a cross-sectional study which collect data in dr. Cipto Mangunkusumo National General Hospital in the year 2017-2018. Patient data collection was obtained through the patient’s medical records, whereas the subjects are women with brain tumors meningioma who have undergone surgery. We found 72 women diagnosed with meningioma; however, only 54 subjects were included in this study. Immunohistochemistry staining were performed to all the 54 subjects and revealed that 53 subjects (98.15%) had positive progesterone receptors and only 1 subject was negative (1.85%). Of the 53 subjects with positive progesterone receptors, 48 subjects used hormonal contraceptive (90.57%), with 43 (89.58%) of them used 3 month injectable contraceptive. There is no correlation between progesterone receptors and the use of hormonal contraceptives in female patients with meningioma brain tumor (p value >0.999, Fisher Test).

Keywords: meningioma, hormonal contraception, progesterone receptor.

Karakteristik dan Korelasi antara Progesteron Reseptor dan Penggunaan Kontrasepsi Hormonal pada Perempuan dengan Meningioma di RSUPN Dr. Cipto Mangunkusumo

Abstrak
Meningioma adalah tumor intrakranial ekstraaksial primer terbanyak dengan perkiraan 30% dari seluruh tumor intrakranial. Penggunaan kontrasepsi hormonal diduga menjadi salah satu faktor risiko meningioma, namun hasil penelitian masih kontroversial. Tujuan penelitian ini adalah mengetahui karakteristik dan korelasi antara progesteron reseptor dan penggunaan kontrasepsi hormonal pada perempuan dengan meningioma. Studi potong lintang ini menggunakan data rekam medis RSUPN dr. Cipto Mangunkusumo pada tahun 2017-2018. Data pasien dikumpulkan melalui rekam medis dimana subyek adalah pasien meningioma intrakranial yang dilakukan operasi. Terdapat 72 perempuan yang didagnosis meningioma, namun data yang dapat dianalisis adalah 54 subyek. Hasil pewarnaan imunohistokimia didapatkan 53 subyek (98.15%) memiliki reseptor progesteron positif. Dari kelompok reseptor progesteron yang positif, 48 subyek (90.57%) menggunakan kontrasepsi hormonal dengan mayoritas (89.58%) menggunakan kontrasepsi injeksi 3 bulan. Tidak didapatkan korelasi antara reseptor progesteron dengan penggunaan kontrasepsi hormonal pada perempuan dengan meningioma (nilai p >0.999, Uji Fisher).

Kata kunci: meningioma, kontrasepsi hormonal, reseptor progesteron.
Introduction
Meningioma is the most common primary, intracranial and extraaxial tumors, covering 30% of all intracranial tumors. Embryologically, meningiomas are derived from neuroectodermal, which came from arachnoid cells (meningothelial, arachnoid cap). Incidence of meningioma is 2.3 to 3.1 cases per 100,000 population/year. On autopsy examination, the incidence of meningioma can reaches for about 3.9 to 5.3 cases per 100,000 population/year. Most of patients with meningioma were adults and elderly, with a high prevalence in women, about 2/3 of the total cases.

The aetiology of meningioma is still not clearly understood. Genetic abnormalities, such as neurofibromatosis and tuberosclerosis, as the risk factors of meningiomas have already been known and studied. The other risk factors associated directly with meningiomas are ionizing radiation. Many external and environmental factors are thought to be risk factors for meningioma, but still, it has not been proven yet. The hormonal factor is thought to be a risk factor for meningioma. Studies have shown contradictory results between hormonal receptors related to risk factors for a brain tumor, including meningioma, but the latest studies showed that progesterone receptors occur in 2/3 of cases of meningioma, and estrogen receptors are present in 1/10 cases of meningioma. Other studies revealed that the risk of meningioma is also increased in the use of non-oral contraceptives, such as implants, and injectable or intrauterine devices.

Hormonal factors in women allegedly have a link with the risk of meningioma. The higher incidence of meningioma in women compared with men, especially during the reproductive period, and the presence of meningioma growth during pregnancy and the luteal phase during menstruation supports this hypothesis.

The presence of an association between hormonal factors and meningioma leads to the use of antihormonal therapy. The use of antiprogesterone such as mifepristone and onapristone, has cytostatic and cytotoxic effects on in vitro cultured meningiomas. Antiprogesterone and antiestrogen therapy have also been performed on recurrent and nonresectable meningiomas, with varying outcomes. The difference in outcomes is caused by differences in hormone levels among individuals undergoing therapy. Based on the results of the study, it can be concluded that hormonal mechanisms have an important role in the effort to prevent and control the growth of meningioma. Therefore, recognizing the characteristics of hormonal receptors in meningiomas needs to be further investigated.

The purpose of this study is to describe the characteristics (demographic, histopathologic, and contraceptive use) and to correlate between positive progesterone receptors and the use of hormonal contraceptives in women diagnosed with meningioma in dr. Cipto Mangunkusumo National General Hospital/Rumah Sakit Umum Pusat Nasional dr. Cipto Mangunkusumo (RSCM).

Methods
This is a cross-sectional study which describes dan correlation between positive progesterone receptors in meningioma IHC staining and the use of hormonal contraceptives in women with a meningioma brain tumor in RSCM. Patient data collection was obtained through the patient’s medical records, whereas the subjects are women with brain tumors meningioma who have undergone surgery. Immunohistochemical staining was performed on the subject who met the criteria. We used bond ready-to-use reagent primary antibody progesterone receptor, with catalogue number: PA0312 to perform the immunohistochemical staining (Figure 1).

Figure 1: Immunohistochemical Staining for Progesterone Receptor (Hematoxylin – Eosin 100 x)

Results
There were 78 patients diagnosed with meningiomas from total of 183 intracranial tumors, consisting of 72 women and 6 men. From a total of 72 subjects (women), as many as 54 subjects met the inclusion criteria. Of the 54 subjects, the median age was 45 (35 – 72) years. Immunohistochemical staining revealed that 53 subjects (98.15%)
had positive progesterone receptors and only 1 subject was negative (1.85%). Of the 53 subjects with positive progesterone receptors, 48 subjects used hormonal contraceptives (90.57%), with 43 (89.58%) of them using a 3-month injectable contraceptive. Only 1 subject used a 1-month injectable contraceptive (Table 1).

Table 1. Demography Characteristics of the Subjects (n=54)

| Characteristics                          | n (%)         |
|------------------------------------------|---------------|
| Age, Median (Min – Max) years            | 45 (35 – 72)  |
| 30 – 40 years                            | 14 (25.9)     |
| 41 – 50 years                            | 30 (55.6)     |
| 51 – 60 years                            | 9 (16.7)      |
| > 61 years                               | 1 (1.8)       |
| Tumor location                           |               |
| Sphenoorbita                             | 30 (55.6)     |
| Non-Sphenoorbita                         | 24 (44.4)     |
| Hormonal contraceptive use               | 48 (88.9)     |
| Pill                                     | 2 (4.2)       |
| 1-month injectable contraceptive         | 1 (2.1)       |
| 3-month injectable contraceptive         | 43 (89.6)     |
| Combination                              | 2 (4.2)       |
| Duration of hormonal contraceptive use   | 10 (1 – 27)   |
| (Median (Min-Max)) years                 |               |
| < 5 years                                | 11 (22.45)    |
| 6 – 10 years                             | 15 (30.61)    |
| 11 – 15 years                            | 12 (24.49)    |
| 15 – 20 years                            | 9 (18.37)     |
| > 20 years                               | 2 (4.08)      |
| Grading WHO                              |               |
| WHO grade I                              | 50 (92.6)     |
| WHO grade II dan III                     | 4 (7.4)       |
| Progesterone Receptor                    |               |
| Positive                                 | 53 (98.2)     |
| Negative                                 | 1 (1.8)       |

Table 2 shows a comparison of hormonal contraception and PR status in meningioma. There is no significant difference between progesterone receptors and the use of hormonal contraceptives in female patients with meningioma brain tumors (p >0.999). Of 48 subjects with positive progesterone receptors that use a hormonal contraceptive, 24 subjects (50%) of them used a 3-month injectable contraceptive. Histopathological findings showed that from 48 subjects that use a hormonal contraceptive, 45 subjects (93.75%) were classified a grade 1 meningioma, with 40 (83.33%) of them using a 3-month injectable contraceptive. According to the location of tumor, the majority of subjects, about 27 (56.25%) were located in the sphenoorbita region and most of them are using a 3-month injectable contraceptive (52,08%). This study also revealed that 15 subjects (31.25%) used a hormonal contraceptive with a duration of 6-10 years with 14 (29,16%) of them using a 3-month injectable contraceptive.

Table 2. Comparative Hormonal Contraception Using and PR Status

| Hormonal Contraception | PR Status | n (%) | p value |
|------------------------|-----------|-------|---------|
|                        | Positive  | Negative |         |
| Yes                    | 48 (98)   | 1 (2)    | >0.999* |
| No                     | 5 (100)   | 0 (0)    |         |
| Total                  | 53 (98.1) | 1 (1.9)  |         |

*Fisher Test

Discussion

Meningioma is the most common type of brain tumor and central nervous system. From this study, 78 cases of meningioma (42.6%) were obtained from a total of 183 cases of brain tumors in the Department of Neurosurgery, RSCM. These results are in line with a report from the 1998-2002 Central Brain Tumor Registry of the United States (CBTRUS) which mentions that there are 19,190 (30.1%) meningiomas cases of a total of 63,698 reported cases of tumors. The study also showed that of a total of 78 meningioma cases, 72 meningiomas were women and only 6 meningiomas were men, with a ratio of 12 to 1. This ratio was higher when compared with studies from Wigertz et al 21 and CBTRUS 1. According to CBTRUS, meningioma cases in women are twice as many as the case in men (6.01 versus 2.75), whereas according to Wigertz et al,21 the ratio of meningioma cases in women compared with men is 2-3 to 1. This indicates that women have certain characteristics and patterns that play an important role in the growth of meningioma. One of the characteristics that contributed to the growth of meningioma is the hormonal factor, whether it is from the inside (endogenous hormone) or outside (exogenous hormone). Meningiomas may be enlarged during pregnancy and the luteal phase of the menstrual cycle (endogenous) and the use of hormonal (exogenous) contraceptives support this statement.15-16

The ratio of women with meningioma higher than in the previous study may be caused by high users of hormonal contraception in Indonesia. According to a National Health study (Risksdas) in 2013, 84.5% of women aged 15-49 years use contraceptives with the majority using injectable hormonal contraceptives (34.3%).22 This confirms
that there is a possible link between hormonal contraceptives and the incidence of meningioma. In this study, almost all subjects had positive progesterone receptors, as many as 53 research subjects (98.15%). Only one subject is negative (1.85%). This figure far exceeds some previous research. Wolfsberger et al reported that 69% of meningioma cases had progesterone receptors, Carrol et al stated that 64% of the meningioma cases had progesterone receptors, and Blakenstein et al found that 75% of the meningioma cases had progesterone receptors. Subjects with positive progesterone receptors are likely to be associated with the location of the tumor because most of the tumors are in the sphenoorbita region (55.56%).

Helseth et al and Klaeboe et al stated that meningioma generally occurs at the age of reproduction. Of the 48 subjects, the majority of subjects were aged 41-50 years old (50%) with the average age of the study subjects being 45.1 years old. Although the majority of subjects are still of productive age (15-49 years), it’s within the limit of productive age. This is likely caused by the overwhelming number of Indonesians who postponed their medical treatment due to certain conditions (eg. traditional medicine) and decide to have treatment later (delayed) when the condition is worst.

Claus et al state that 90% of meningiomas are benign (grade 1). This study shows similar results in which most of the study subjects were grade 1 meningioma - 50 subjects (92.59%). No subjects with grade 3 meningioma alone. Of the four remaining subjects (7.41%), each consisting of grade 2 meningioma, and mixed-type meningioma (grade 1 and 2 meningiomas; grade 2, 3 meningiomas; grade 1, 2, 3 meningiomas) each consist of 1 subject, all of which are categorized as atypical/borderline meningiomas. This is also in line with data from Claus et al that there is a total of 5%, atypical/borderline meningiomas, and 3-5% malignant meningiomas.

Of all meningiomas, 15-20% of them were found in the sphenoid wing with hyperostosis in the frontotemporal-lateral region of the orbit (sphenoorbita meningioma). The study at RSCM showed different results. The study at RSCM in 2013 showed that there were 60 patients with sphenoorbita meningioma with hyperostosis (46.1%) of 130 patients with intracranial meningioma in 2010-2012. Similar results are also shown in this study, 30 subjects (55.56%) located in sphenoorbita region. This difference is probably caused by the distribution of patients at this hospital which is different from most of the literature because RSCM is the highest referral hospital in Indonesia where patients undergoing treatment at this hospital are referral patients that cannot be handled at the previous hospital. Therefore, a multicenter study needs to be held for further investigation of this issue.

Of the 53 subjects with positive progesterone, most of them had histological findings of grade 1 meningioma, 50 subjects (94.33%). This is also in accordance with the research of Wolfsberger et al which states that progesterone receptors are more commonly found in grade 1 meningioma. One subject with a negative progesterone receptor, has a higher histological grading, which was grade 2-3 meningioma. This is in line with Roser et al study which states that the absence of progesterone receptors correlates with higher tumor grading. This suggests that there is a certain connection between the presence of progesterone receptors and the growth of meningiomas. Therefore, a thorough evaluation of the biomolecular mechanism of the occurrence of meningioma is required.

Of the 53 subjects of women with a positive progesterone receptor, 48 subjects of them were using hormonal contraceptives (90.57%), and 43 subjects use a 3-month injectable contraceptive (89.58%). This is in line with the study conducted by Wigertz et al which examined 185 cases of meningioma in women aged 20 to 69 years, and found that the use of hormonal contraceptives such as contraceptive injection, implant or hormonal IUD increased the risk of meningioma incidence as much as 1.5 times.

This study also revealed that 15 subjects (31.25%) were using hormonal contraceptives with a duration of 6-10 years with 14 (29.16%) of them using 3-month injectable contraceptives. This is different from Supartoto et al who stated that the use of hormonal contraceptives for more than 10 years has a higher risk than the occurrence of meningioma. This suggests that there is the use of hormonal contraceptives for minimum duration of 6 years has a high risk for the occurrence of meningioma.

The limitation of this study is almost all our subjects used hormonal contraception and almost all had positive PR status. This imbalance of subject numbers in both variables could be a bias of the study.

**Conclusion**

This study showed that there is no correlation between progesterone receptors and the use of hormonal contraceptives in female patients with a meningioma brain tumor.

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