Research Article

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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Received 21 April 2022; Accepted 24 August 2022
http://doi.org/10.23886/ejki.10.161.101

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 dikumpuikan melalui rekam medis dimana subyek adalah pasien meningioma intrakranial yang dilakukan operasi. Terdapat 72 perempuan yang didiagnosis 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).[1] 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.[2,3]

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.[5-9] 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. Several studies have shown contradictory results between hormonal receptors related to risk factors for a brain tumor, including meningioma, but the latest study showed that progesterone receptors occur in 2/3 of cases of meningioma, and estrogen receptors are present in 1/10 cases of meningioma.[4,10-12] 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.[13]

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.[13-16]

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 cytocidal effects on in vitro cultured meningiomas.[17] Antiprogesterone and antiestrogen therapy have also been performed on recurrent and nonresectable meningiomas, with varying outcomes.[18-20] 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[16], with catalogue number: PA0312 to perform the immunohistochemical staining (Figure 1).

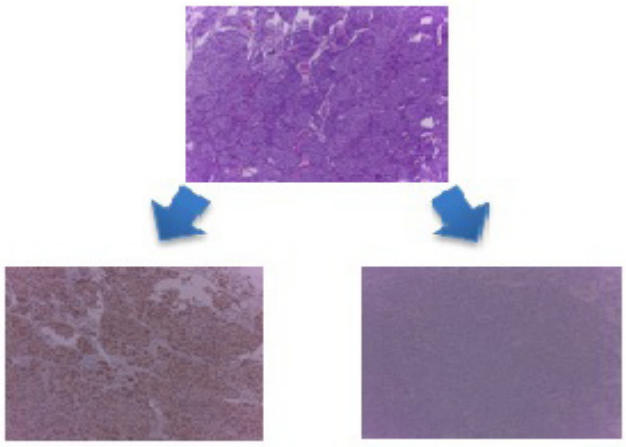

Figure 1. Immunohistochemical Staining for Progesterone Receptor (Hematoxylin – Eosin 100 x)

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 (Median (Min-Max)) years	10 (1 – 27)
< 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.[1] 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 (Riskesdas) 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[21] reported that 69% of meningioma cases had progesterone receptors,[25] Carrol et al[27] stated that 64% of the meningioma cases had progesterone receptors,[26] and Blakenstein et al[26] found that 75% of the meningioma cases had progesterone receptors.[27] 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[13] and Klaeboe et al[14] stated that meningioma generally occurs at the age of reproduction.[13-14] 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), [22] 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[23] state that 90% of meningiomas are benign (grade 1).[23] 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[23] that there is a total of 5%, atypical/borderline meningiomas, and 3-5% malignant meningiomas.[23]

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.[24] 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[25] which states that progesterone receptors are more commonly found in grade 1 meningioma.[25] 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[28] study which states that the absence of progesterone receptors correlates with higher tumor grading.[28] 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,[21] 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[29] 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 the use of hormonal contraceptives with a 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.

Acknowledgement

There is no conflict of interest in this study.

Reference

1. CBTRUS. Statistical report: Primary brains tumors in the United States, 1998–2002. Illinois: The Central Brain Tumor Registry of the United States; 2005
2. Goldstein RA, Jorden MA, Harsh IV. Meningiomas: natural history, diagnosis and imaging. Philadelphia: Lippincott, Williams & Wilkins, 2005
3. Kuratsu J. Kochi M. Ushio Y. Incidence and clinical features of asymptomatic meningiomas. J Neurosurg. 2000;92: 766-70. doi: 10.3171/jns.2000.92.5.0766
4. Hatch EE, Linet MS, Zhang J, Fine HA, Shapiro WR, Selker RG, et al. Reproductive and hormonal factors and risk of brain tumors in adult females. Int J Cancer. 2005;114:797–805. doi: 10.1002/ijc.20776.
5. Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. Epidemiol Rev 1995;17:382–414. oi: 10.1093/oxfordjournals.epirev.a036200,
6. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-Oncol. 2002;4:278–99. doi: 10.1093/neuonc/4.4.278.
7. Ron E, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med. 1988;319:1033–9. doi: 10.1056/NEJM198810203191601.
8. Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A, et al. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. Radiat Res. 1998;150:357–64.
9. Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst. 2002;94:1555–63. doi: 10.1093/jnci/94.20.1555.
10. Schlehofer B, Blettner M, Preston-Martin S, Niehoff D, Wahrendorf J, Arslan A, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer. 1999;82:155–60. doi: 10.1002/(sici)1097-0215(19990719)82:2<155::aid-ijc1>3.0.co;2-p.
11. Jhawar BS, Fuchs CS, Colditz GA Stampfer MJ. Sex steroid hormone exposures and risk for meningioma. J Neurosurg. 2003;99:848–53. doi: 10.3171/jns.2003.99.5.0848.
12. Huang K, Whelan EA, Ruder AM, Ward EM, Deddens JA, Davis-King KE, et al. Reproductive factors and risk of glioma in women. Cancer Epidemiol Biomarkers Prev. 2004;13:1583–8.
13. Helseth A. Incidence and survival of intracranial meningioma patients in Norway 1963–1992. Neuroepidemiology. 1997;16:53–9. doi: 10.1159/000109671.
14. Klaeboe L, Lonn S, Scheie D, Auvinen A, Christensen HC, Feychting M, et al. Incidence of intracranial meningiomas in Denmark, Finland, Norway and Sweden, 1968–1997. Int J Cancer. 2005;117:996–1001. doi: 10.1002/ijc.21255.
15. Casabella AM, Urakov TM, Basil G, Morcos JJ. Management of Foramen Magnum Meningioma During Pregnancy: Literature Review and Case Report. World Neurosurg. 2017;97:752.e15-8. doi: 10.1016/j.wneu.2016.10.058 .
16. Bonfield CM, Engh JA. Pregnancy and brain tumors. Neurol Clin. 2012;30:937-46. doi: 10.1016/j.ncl.2012.04.003.
17. Matsuda Y, Kawamoto K, Kiya K, Kurisu K, Sugiyama K, Ouzumi T. Antitumor effects of antiprogesterones on human meningioma cells in vitro and in vivo. J Neurosurg. 1994;80:527–34. doi: 10.3171/jns.1994.80.3.0527.
18. Grunberg SM, Weiss MH, Spitz IM, Ahmadi J, Sadun A, Russell CA, et al. Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. J Neurosurg. 1991;74:861–6. doi: 10.3171/jns.1991.74.6.0861.
19. Touat M, Lombardi G, Farina P, Kalamarides M, Sanson M. Successful treatment of multiple intracranial meningiomas with the antiprogesterone receptor agent mifepristone (RU486). Acta Neurochir (Wien). 2014;156:1831-5. doi: 10.1007/s00701-014-2188-4.
20. Altinoz MA. Tamoxifen prevention of meningioma and its proposal for the treatment of meningioma. Revisiting old data in the light of recent epidemiological observations. Eur J Cancer Prev. 2021 Sep 1;30(5):409-412. doi: 10.1097/CEJ.0000000000000634 .
21. Wigertz AA, Lönn SS, Mathiesen TT, Ahlbom AA, Hall PP, and Feychting MM. Risk of brain tumors associated with exposure to exogenous female sex hormones. Am J Epidemiol. 2006;164:629-36. doi: 10.1093/aje/kwj254.
22. Riset Kesehatan Dasar. Tingkat pencapaian KB. Departemen Kesehatan Republik Indonesia tahun 2013. Jakarta: Departemen Kesehatan Republik Indonesia; 2013. Indonesian.
23. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. J Neurooncol. 2010 Sep;99(3):307-14. doi: 10.1007/s11060-010-0386-3. Epub 2010 Sep 7. PMID: 20821343
24. Aman RA, Wicaksono A. Penelitian retrospektif mengenai hubungan antara pengguna kontrasepsi injeksi dengan hasil operasi, komplikasi dan rekurensi padapasien dengan *sphenoid wing* meningioma dengan hiperostosis di Rumah Sakit Cipto Mangunkusumo periode 2010-2012. Jakarta: Universitas Indonesia; 2013. Indonesian.
25. Wolfsberger SS, Doostkam SS, Boecher-Schwarz HGH-G, Roessler K, Trotsenburg MV, Hainfellner JA, et al. Progesterone-receptor index in meningiomas: correlation with clinico-pathological parameters and review of the literature. Neurosurg Rev. 2004;27:238–45. oi: 10.1007/s10143-004-0340-y.
26. Blankenstein MA, Verheijen FM, Jacobs JM, Donker TH, van Duijnhoven MW, Thijssen JH. Occurrence, regulation, and significance of progesterone receptors in human meningioma. Steroids. 2000;65:795–800. doi: 10.1016/s0039-128x(00)00193-8.

27. Carroll RS, Glowacka DD, Dashner KK, Black PM. Progesterone receptor expression in meningiomas. Cancer Res. 1993;53: 1312–6.
28. Roser FF, Nakamura MM, Bellinzona MM, Rosahl SK, Ostertag HH, Samii MM. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol. 2004;57:1033–7. doi: 10.1136/jcp.2004.018333.
29. Supartoto A, Mahayana IT, Christine RN, Suhardjo, Agni AN, Sasongko MB.. Exposure to Exogenous Female Sex Hormones is Associated with Increased Risk Oforbito-Cranial Meningioma in Females: A Case-Control Study. Int J Ophthalmic Pathol. 2016.;5. *doi:10.4172/2324-8599.1000183.*