ABSTRACT

Neurofibromatosis type 2 (NF2) gene mutation and progesterone receptor mRNA expression in the pathogenesis of sporadic orbitocranial meningioma

Indra Tri Mahayana[1], Agus Supartoto[1], Suhardjo[1], Didik Setyo Heriyanto[2]

1. Department of Ophthalmology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito General Hospital, Yogyakarta
2. Department of Pathological Anatomy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito General Hospital, Yogyakarta

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Introduction and objective
Merlin, a protein of Neurofibromatosis type 2 (NF2) gene, has an important role to strengthen intercellular adhesion that prevents tumor progression. Progesterone receptor (PR) status associated with gene mutations on chromosome 22 (where the NF2 gene resides) is responsible in the incidence of meningioma. This study was aimed to investigate the role of NF2 gene mutation in the pathogenesis of sporadic orbitocranial meningioma and its association with PR expression.
Methods
This was a case-control study (positive NF2 mutation vs non-mutation). Thirty-four sporadic meningioma patients (confirmed by histopathological examination) with no familial NF2-related meningioma history were recruited. They were interviewed for their obstetric, gynecologic, and contraception history. mRNA PR investigation was performed with Real-Time PCR. NF2 mutation was investigated using Qbiomarker Somatic Mutation PCR Assay after its cDNA extraction (Four cytoband coordinates: c 634C>T/pQ212, c 655G>A/pV219M, c 784C>T/pR262 and c 1228C>T/pQ410).
Results
NF2 gene mutation was found in 35.29% patients. Control group was strongly associated with exogenous hormonal exposure (mutation vs non-mutation: 83.3 vs 95.5%, $p < 0.001$). PR was found significantly lower in control group ($p= 0.033$) which resembled as long term exogenous progesterone exposure. However, case group was associated with higher rate of progression to grade II (mutation vs non-mutation, 18.2 vs 5%, $p <0.001$) and was associated more in fibrous and anaplastic tumor tissue.
Conclusion
Meningioma pathogenesis was not only dependent on NF2 mutation, but also strongly associated with exogenous progesterone exposure. Benign to malignant meningioma progression was found to be due to NF2 mutation.

Keywords: Orbitocranial meningioma, Neurofibromatosis type 2, Progesterone receptor, Hormonal contraception, Real time PCR

INTISARI

Hubungan mutasi gen Neurofibromatosis 2 (NF2) dengan ekspresi reseptor progesteron dan estrogen pada jaringan meningioma orbitokranial sporadis

Indra Tri Mahayana[1], Agus Supartoto[1], Suhardjo[1], Didik Setyo Heriyanto[2]

1. Departemen Ilmu Kesehatan Mata, Fakultas Kedokteran, Kesehatan Masyarakat dan Keperawatan, Universitas Gadjah Mada, Yogyakarta, Indonesia
2. Departemen Ilmu Patologi Anatomi, Fakultas Kedokteran, Kesehatan Masyarakat dan Keperawatan, Universitas Gadjah Mada, Yogyakarta, Indonesia

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Pendahuluan
Gen neurofibromatosis tipe 2 (NF2) bertanggung jawab pada produksi protein merlin yang memiliki peran penting untuk memperkuat adhesi antar sel yang mencegah perkembangan tumor. Status progesterone receptor (PR) terkait dengan mutasi gen pada kromosom 22 (di mana gen NF2 berada) yang bertanggung jawab dalam kejadian meningioma. Penelitian ini bertujuan untuk mengetahui peran mutasi gen NF2 dalam patogenesis meningioma orbitokranial sporadis dan hubungannya dengan ekspresi PR.

Metode
Desain penelitian ini adalah kasus-kontrol (mutasi NF2 positif vs non-mutasi). Penelitian dilakukan pada 34 pasien meningioma sporadis (dikonfirmasi dengan pemeriksaan histopatologi) tanpa riwayat meningioma NF2 familial. Wawancara dilakukan untuk menggali riwayat obstetrik, ginekologi, dan penggunaan kontrasepsi. Pemeriksaan mRNA PR dilakukan dengan Real-Time PCR. Mutasi NF2 diselidiki menggunakan Qbiomarker Somatic Mutation PCR Assay setelah ekstraksi cDNA (*cytoband coordinate*: c 634C> T / pQ212, c 655G> A / pV219M, c 784C> T / pR262 dan c 1228C> T / pQ410).

Hasil
Mutasi gen NF2 ditemukan pada 35,29% pasien. Kelompok non-mutasi berhubungan dengan paparan hormonal eksogen (mutasi vs non-mutasi: 83,3 vs 95,5%, p <0,001). PR ditemukan secara signifikan lebih rendah pada kelompok non-mutasi (p = 0,033) yang dapat didasari sebagai akibat paparan progesteron eksogen jangka panjang. Kelompok mutasi berhubungan dengan progresifitas meningioma yang lebih tinggi (mutasi vs non-mutasi, 18,2 vs 5%, p <0,001) dan berhubungan dengan jenis histologis fibrosa dan anaplastik.

Kesimpulan
Tumorigenesis meningioma tidak hanya didasari adanya mutasi NF2, tetapi juga berhubungan dengan paparan progesteron eksogen. Perkembangan meningioma dari jinak ke ganas ditemukan akibat mutasi NF2.

Kata kunci: meningioma orbitocranial, Neurofibromatosis tipe 2, reseptor progesteron, kontrasepsi hormonal, Real time PCR