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“Meeting the Challenges, Facing the Future”
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Dear Friends,

It is our great pleasure to invite you to The 5th WFNS Spine Committee Biennial Conference of WFNS which will be held at Bali, Indonesia between October 25th - 27th, 2018.

WFNS scientific committees try to contribute to the education and progress of sub disciplines of neurosurgery. Spine surgery is getting a high interest and Spine Committee Symposia every two years are the largest activity of the committee. I am happy to invite you to Bali, Indonesia to endorse activities in this part of the world. This meeting will be in conjunction with the Annual Meeting of Indonesian Neurological Society, Asian Epilepsy Surgery Congress.

On October 25, a one-day cadaver dissection course will be held in Surabaya. The meeting aims to reach a large number of audience, thus contribute to the spine education in this area more effectively. There will be “intense”, and full of excellent lectures from prominent experts, results of implementation of new procedures, case discussions, debate sessions, video demonstrations, and workshops from industry.

The location of our congress is Bali island, one of the most beautiful and exotic place of the world. We really hope that it will endow us with many precious and long-lasting memories to cherish.

We look forward to seeing you in Bali in October 2018.

Co-chairman of the WFNS Spine Committee.

Mehmet Zileli  Michael G.Fehlings  Daniel J.Hoh

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**WELCOME MESSAGE**

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Co-chairman of the WFNS Spine Committee.
THE EFFECT OF CURCUMIN EXTRACT TOWARD MATURE BRAIN DERIVED NEUROTrophic FACTOR (M-BDNF) EXPRESSION AFTER TRAUMATIC BRAIN INJURY

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Department of Neurosurgery, Universitas Sumatera Utara/ Haji Adam Malik Hospital Medan, Indonesia

Background: Traumatic Brain Injury (TBI) causes disability, death and huge economic losses in various countries of the world. TBI incident varies between 67 –317 per 100.000 population, with 4-7% mortality rate in moderate brain injury, and 50% in severe brain injury. The mature BDNF (m-BDNF) pathway system is a potential therapeutic target for neurological disorders in traumatic brain injury. Curcumin extract has a neuromodulatory effect which has a modulation effect on the expression and activation of the m-BDNF system in the hippocampus area.

Methods: Laboratory experimental study in Faculty of medicine University of Brawijaya which used thirty male Sprague-Dawley rats. Rats were divided into three treatment groups, group A (negative control), group B given traumatic brain injury, group C given traumatic brain injury and Curcumin administration. Rats’ brain tissue was immunohistochemically processed, to observe the number of cells expressing m-BDNF in the subgranular zone (SGZ) of the hippocampus dentate gyrus (DG). Data were analyzed with SPSS and ANOVA analysis.

Result: In ANOVA analysis, mean expression of m-BDNF group C compared to group A and group B were increased significantly (p=0.0001). Curcumin Through Induction of m-BDNF and activation of its intracellular receptor TrkB can produce neural regeneration, reconnection, and dendritic sprouting, and can enhance synaptic efficacy.

Conclusion: Curcumin can increase the expression of m-BDNF in the subgranular zone of the hippocampus dentate gyrus.

Keywords: Curcumin, TBI, m-BDNF, Neuroplasticity
CORRELATION BETWEEN HUMAN EPIDERMAL GROWTH FACTOR 2 (HER 2) EXPRESSION WITH HISTOPATHOLOGICAL LEVEL ON INTRACRANIAL MENINGIOMA PATIENTS AT HAJI ADAM MALIK HOSPITAL MEDAN INDONESIA

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Department of Neurosurgery, Faculty of Medicine University of Sumatera Utara, Indonesia

Abstract
Background: Meningiomas are the most common intracranial primary neoplasm in adults. Meningiomas arise from the arachnoidal cells surrounding the brain and are one of the most common tumors of the central nervous system. Meningiomas account for about 15-30% of all primary intracranial tumors. According to the 2007 WHO classification, meningiomas are divided into three grades (I, II and III). Several studies have reported higher recurrence rates for males than for females. However, other studies have found no significant difference based on gender and no association between tumor development in young patients (< 40 yrs) and a high likelihood of recurrence. However, some study found a significant difference between age and recurrence. The aggressiveness of meningiomas is unpredictable. HER2 represents a well-known prognostic factor in various tumors such as breast carcinomas. There are only a few studies on the relationship between meningioma and HER2 expression, and the results are different as well. The aim of this study was to determine this relationship.

Methods: this study was a crosssectional analytic study of 32 parafin block meningioma after staining with HER 2.

Result: The result from this study has significant result from expression HER 2 in intracranial meningiomas.

Conclusion: HER 2 expression plays a role in the development of more-aggressive meningiomas or not is a question that needs to be clarified in further studies. The results of our case report did not advocate this role for HER2.

Introduction
Meningiomas are the most common intracranial primary neoplasm in adults. Meningiomas arise from the arachnoidal cells surrounding the brain and are one of the most common tumors of the central nervous system. Meningiomas account for about 15-30% of all primary intracranial tumors. According to the 2007 WHO classification, meningiomas are divided into three grades (I, II and III). With this new grading system, which includes the brain invasion into the diagnostic criteria for aggressiveness, the percentage of atypical meningiomas grew to 20–35% of newly diagnosed meningiomas. This classification is important because, together with the extension of resection, it may help in predicting the recurrence rate and thus the global prognosis.
Human epidermal growth factor receptor-2 (HER2/neu, c-erbB2), one of a family of four membrane tyrosine kinases, was found to be amplified in a human breast cancer cell line twenty five years ago, and this amplification was shown to be important in the pathogenesis and progression of human breast cancer two years later. Since that time, HER2 amplification and resultant HER2 protein overexpression have been linked to important tumor cell proliferation and survival pathways; several drugs have been developed to target the pathway; and, the detection of HER2 has become a routine prognostic and predictive factor in breast cancer. HER2 is a membrane tyrosine kinase and oncogene that is overexpressed and gene amplified in about 20% of breast cancers. When activated it provides the cell with potent proliferative and anti-apoptosis signals and it is the major driver of tumor development and progression for this subset of breast cancer. When shown to be overexpressed or amplified by appropriate methods, HER2 is a valuable treatment target.

The estrogen receptor (ER) and the HER2 (c-erbB2, HER2/neu) signaling pathways are the dominant drivers of cell proliferation and survival in the majority (85%) of breast cancers. Targeting these pathways provides the most effective therapy in appropriately selected patients. Endocrine therapy to target ER and trastuzumab to target HER2 provide striking disease-free and overall survival benefits in the adjuvant setting when micrometastatic disease is present (50% reduction in risk of recurrence). Remissions sometimes lasting years, although temporary, are seen in patients with metastatic disease treated with ER- and HER2-targeted therapy, the later usually combined with chemotherapy.

The HER2 pathway has been described in systems biology terms as a complex biological network comprised of three layers, an input layer of membrane receptors and their ligands to trigger the signal coming from outside the cell, a core system processing layer of protein kinases transmitting the signal to the nucleus, and an output layer of transcription factors regulating genes that affect various cellular functions. In turn, the genes and gene products regulating the activity of the pathway have been and are being defined. The input layer is comprised of 4 membrane receptors/tyrosine kinases (TKs) (HER1–4) and their many ligands.

In breast cancer, HER2 is the dominant TK receptor, being amplified in
20% of cases. Upon ligand binding to their extracellular domains, HER proteins undergo dimerization and transphosphorylation of their intracellular domains. HER2 does not have a ligand and relies on heterodimerization with another.

Figure. 1 HER signaling network and HER2-targeted therapy in breast cancer.

Family member or homodimerization with itself when expressed at very high levels to be activated. These phosphorylated tyrosine residues dock with numerous intracellular signaling molecules leading to activation of downstream second messenger pathways and crosstalk with other membrane signaling pathways.

Transcription factors activated by the pathway regulate many genes involved in cell proliferation, survival, differentiation, angiogenesis, and invasion and metastasis. HER2 has the strongest catalytic kinase activity and HER2 containing heterodimers have the strongest signaling activity. HER2 exists in an open conformation exposing its dimerization domains making it the dimerization partner of choice among the family members. HER3 is activated by ligand (heregulin) binding but it lacks TK activity, and, like HER2, must partner with another family member to be activated. Nevertheless, it has multiple docking sites for PI3K and when heterodimerized with
HER2 is the most potent stimulator of the PI3K/AKT anti-apoptosis pathway.

HER2 can also be activated by complexing with other membrane receptors such as insulin-like growth factor receptor 1. Even estrogen, working via the non-genomic activity of ER outside the nucleus has been shown to activate HER2 signaling. An aberrant form of HER2 missing the extracellular domain, so-called p95, is found in some breast cancers. p95 is constitutively active since the external domain of these receptors acts as an inhibitor until they are bound by ligand. p95 can cause resistance to trastuzumab, an antibody that works by binding to a domain in the external domain of HER2. This domain is missing in p95. p95 is not detected by antibodies that target the external domain of HER2 for the same reason.

Normal tissues have a low complement of HER2 membrane protein. Overexpression of HER2 is seen in 20% of breast and in some ovarian and gastric cancers, and it confers worse biological behavior and clinical aggressiveness in breast cancer. Breast cancers can have up to 25–50 copies of the HER2 gene, and up to 40–100 fold increase in HER2 protein resulting in 2 million receptors expressed at the tumor cell surface. The differential in HER2 expression between normal tissues and tumors helps to define HER2 as an ideal treatment target. Trastuzumab, the first treatment targeting HER2, is well-tolerated in patients with little toxicity, since its effects are relatively specific for cancer cells overexpressing HER2.

Predicting the biological and clinical behaviour of meningiomas remains a significant problem. Currently, the most reliable factors that are helpful in predicting recurrence of meningiomas are the extent of surgical resection and histological grade. Atypical and anaplastic meningiomas are known to be associated with aggressive behaviour and poor outcome. However, even for histologically benign meningiomas, clinical behaviour cannot always be predicted with accuracy, because some of them recur, even after complete surgical resection. Therefore, numerous efforts have been made for the evaluation of other factors that would aid prediction of recurrence of benign meningiomas. Previous studies have investigated the role of proliferative index (PI), and hormonal receptors in predicting the behaviour of meningiomas. Others have investigated the expression of apoptosis regulating proteins and HER2 in meningiomas. However, very limited data have been published on the relationship
between these factors and their association with recurrence of benign meningiomas.

Predicting the biological and clinical behavior of meningiomas remains a significant problem. Currently, the most reliable factors that are helpful in predicting recurrence of meningiomas are the extent of surgical resection and histological grade.

The aggressiveness of meningiomas is unpredictable. HER2 represents a well-known prognostic factor in various tumors such as breast carcinomas. There are only a few studies on the relationship between meningioma and HER2 expression, and the results are different as well. The aim of this study was to determine this relationship.

**Materials and Methods**

This is a retrospective study of primary intracranial meningiomas diagnosed in the Department of Pathology, University of Sumatera Utara. This study start January 2018 – September 2018. The study was approved by the Institutional Ethics Committee (No.405/TGL/KEPK FK USU-RSU HAM/2018). The clinical details of the patients were noted from the computerized hospital information system. The tumor tissue samples fixed in 10% neutral-buffered formalin and paraffin-embedded tissue blocks were cut into 4–5 microns. Two pathologists independently reviewed the hematoxylin and eosin–stained slides, confirmed the diagnosis according to the 2007 WHO classification system, and classified the histological subtypes and grading of the meningiomas. All the patients received regular follow-up after surgery, without postoperative chemoradiation therapy. The recurrence-free survival (RFS) was calculated from the time of surgery to the first suspected recurrence of meningioma. Evidence of tumor recurrence was provided by a computed tomography scan or a magnetic resonance image showing a meningioma in a location contiguous with the previous operation site. Based on pathologic result, we performed an immunohistochemical staining with HER2, 32 blocks of meningioma were selected, and immunohistochemical staining was then performed for each specimen. We use c-erbB-2 Oncoprotein (SP3) Rabbit Monoclonal Antibody with catalog number RMAB008R manufactured by Diagnostic BioSistems.
Result
There were a total of 32 cases of meningiomas during the study period. There were 25 females and 7 males with female to male ratio of 3:1 and the mean age was 44.59 years (range: 32-60 years) show in table 1. Among the 32 cases of meningioma, Grade I were 81.3, Grade II 12.5, and Grade III 6.3. Table 2.

<table>
<thead>
<tr>
<th>Age-Group</th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>20 - 29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30 - 39</td>
<td>10</td>
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<td>40 - 49</td>
<td>13</td>
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<tr>
<td>50 - 59</td>
<td>7</td>
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<td>60 - 69</td>
<td>2</td>
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<tr>
<td>70 - 79</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>100</td>
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Table 1. Distribution frequency Age-Group

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>n</th>
<th>%</th>
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<tr>
<td>WHO Grade 1</td>
<td>26</td>
<td>81.3</td>
</tr>
<tr>
<td>WHO Grade 2</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>WHO Grade 3</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>100.0</td>
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</table>

Table 2. Distribution frequency based on WHO Grading

Most common intracranial location was parasagittal meningioma, and most common pathological result was meningothelial meningioma. Positivity or expression of HER2/neu in overall females and males was 44 % and 57.1%, respectively, which is not statistically significant including those of Grade I and Grade II/III meningiomas. Statistically significant relationship was not found
between the positivity of HER2/neu in intracranial meningiomas. The positivity of HER2/neu within the Grade I (25%) was higher than that in the Grade II (18.7%) and Grade III (9.37%) meningiomas. Figure 2.

![Figure 2. Immunohistochemical staining from HER2](image)

We used Spearman’s rho test, sig value 0.001, show have a significant correlation between expression HER2 with meningiomas. Correlation coefficient 0.547, show have a moderately strong correlation.

**Discussion**

HER2 is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of cancer.

HER2 (also known as erbB-2) is a 185-kD transmembrane glycoprotein with tyrosine kinase activity. These tumors are known to be hormonally modulated and may occur in association with breast carcinoma.

HER2 is highly expressed in a significant proportion of breast cancer, ovarian cancer, and gastric cancer. Since the discovery of its role in tumorigenesis, HER2 has received great attention in cancer research during the past two decades. HER-2 is a type of oncogene in human carcinoma, and many studies have indicated HER-2 overexpression in several types of cancer and is associated with a particularly aggressive form of the disease. In a study performed by Loussouran et al. HER2 immunostaining was detected in 10 (28.5%) of 35 meningiomas. They also reported a significantly higher rate of tumor recurrence in HER2 positive than in HER2-negative meningiomas. They used different methods for assessment of HER2 immunoreactivity.

In 2010, Wang et al. showed that high levels of HER2 expression correlated with increase of tumor grades and
recurrence in meningiomas. There are only a few studies on HER2 expression in meningiomas. Torp et al. reported a higher ratio (63%) of HER2-positive meningiomas, but they applied immunostaining on frozen sections. They investigated a very small number of meningiomas and reported HER2 positivity in 12 of the 19 patients. While Andersson et al. demonstrated a high rate of HER2 expression in meningiomas, Potti et al. reported a very low rate of it in the same year and suggested that HER2 overexpression has no role as a prognostic factor in meningiomas.

**Conclusion**

HER2 expression plays a role in the development of more-aggressive meningiomas or not is a question that needs to be clarified in further studies. The results of our case report did not advocate this role for HER2.

For the HER2 targeted cancer therapy, numerous strategies including the blockage of receptor dimerization, inhibition of the tyrosine kinase activity, and interruption of the downstream signal pathway will be summarized. For the targeted drug delivery to HER2 positive tumor cells, various targeting ligands and their delivery systems will be described in details.

Successful development of the humanized monoclonal anti-HER2 antibody (Trastuzumab) for the treatment of breast cancer further spurred scientists to develop various HER2 specific antibodies, dimerization inhibitors and kinase inhibitors for cancer therapy.

On the other hand, the high expression of HER2 and the accessibility of its extracellular domain make HER2 an ideal target for the targeted delivery of anti-tumor drugs as well as imaging agents.

**Competing interest**

The authors declare no competing interest.

**Authors’ contributions**

The author read and approved the final version of the manuscript.
References


