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ASSOCIATION BETWEEN AGES AND GLUCOCORTICOID-INDUCED DIABETES MELLITUS INCIDENCE IN INTRACRANIAL TUMOR PATIENTS

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Abstract
Background: glucocorticoids are the main therapy for treating peritumoral edema in patients with intracranial tumors. The use of glucocorticoids has side effects, one of which is hyperglycemia or what is called Glucocorticoid-Induced Diabetes Mellitus (GIDM). Hyperglycemia in brain tumor patients is associated with decreased survival, increased recurrence and degeneration to malignancy.
Objective: to determine the association between age and the incidence of GIDM in intracranial tumor patients.
Method: this study uses a cohort design. Sampling was conducted at Ruang Rawat Inap Terpadu (Rindu) H. Adam Malik General Hospital Medan. Samples were taken as many as 30 subjects consecutively. Blood sugar levels were checked twice a day on days 4 and day 5. Data analysis used the fisher test and eta correlation test.
Results: demographic characteristics of the study subjects were an average age of 51 years, high school education level, housewife occupation. As many as 46.7% were primary brain tumors and 53.3% were metastatic brain tumors with the most metastases originating from the lungs (56.3%). There was no difference in the proportion of age groups for the incidence of GIDM ($p > 0.05$). There was no significant relationship between age and the incidence of GIDM ($p > 0.05$).
Conclusion: there is no difference in the proportion of the age group to the incidence of GIDM and there is no significant association between age and the incidence of GIDM.

Introduction
In brain tumor patients, glucocorticoids are the main therapy for treating peritumoral edema.[1] Corticosteroids have been widely used in tumor therapy and are useful in brain tumor patients with significant peritumoral edema accompanied by neurological deficits.[2] The recommended agent is dexamethasone with an intravenous bolus dose of 10 mg followed by a maintenance dose of 16-20 mg / day intravenously then tappering off 2 - 16 mg (in divided doses) depending on clinical.[3] Dexamethasone decreases the expression of Vascular Endothelial Growth Factor (VEGF) through the activation of glucocorticoid receptors thereby improving brain blood barrier barrier dysfunction.[4]

The use of steroids has side effects, one of which is hyperglycemia.[5] In the use of steroids in hospitals found evidence that half of the patients who get high doses of steroids will experience hyperglycemia. Hyperglycemia is reported in 72% of primary brain tumor patients receiving dexamethasone therapy.[6] Steroids cause hyperglycemia both in people with diabetes mellitus (DM) and can cause DM in patients without a history of increase previous glucose level or called Glucocorticoid-Induced Diabetes Mellitus (GIDM). Glucocorticoid-Induced Diabetes Mellitus is defined as an increase in blood sugar levels due to the use of glucocorticoids in patients with or without a history of previous DM.[5]

One of the main risk factors that cause GIDM is age.[7] The results of the study by Katsuyama et al (2015) stated that patients aged > 65 years had a risk of developing GIDM by 2.95 times greater than patients aged <65 years.[8] Kim et al (2011) concluded that old age was the only risk factor for GIDM.[9] Liu et al (2014) say that the elderly population has a GIDM incidence of 12%.[10]

Method

Study sample
The study sample was taken from patients with intracranial tumors in Adam Malik General Hospital Medan with consecutive sampling techniques. The research subjects consisted of 30 intracranial tumors patients who received steroid therapy and willing to take part in the study by signing a research informed consent sheet.

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Study design
This study is a cohort design without treatment. The diagnosis of intracranial tumors is based on history, physical examination and head computed tomography scan (CT scan).

Statistical analysis
Data from the research were analyzed statistically using the SPSS Windows computer program (Statistical Product and Science Service) version 22.0. To analyze the relationship between research variables, in this case to determine the association between ages and glucocorticoid induced diabetes mellitus with eta correlation test and to determine proportion of the age group to the incidence of glucocorticoid induced diabetes mellitus with fisher test.

Result

Patients with intracranial tumors who received steroid therapy at H. Adam Malik Hospital Medan in January until March 2020, there were 30 patients with intracranial tumors who participated in the study.

Based on the characteristics of 30 research subjects, the age of all research subjects had a mean of 51 ± 2.85 years. Research subjects aged <65 years were 21 subjects (70%) and> 65 years were 9 subjects (30%). The research subjects were 15 male subjects (50%) and 15 female subjects (50%). The education level of the most research subjects was Senior Secondary School, as many as 17 subjects (56.7%) and at least Diploma as many as 1 subject (3.3%). Respondents occupations were mostly housewives with 11 subjects (36.7%) and at least 1 private employee (3.3%). Research subjects who experienced GIDM were 11 subjects (36.7%) and not GIDM were 19 subjects (63.3%). For complete data about the characteristics of the subject of this study are presented in table 1 below.

Table 1. Demographic Characteristics of Research Subjects (n = 30)

Characteristics	Frequency n=30	Percentage (%)
Age,average ± SD (years)	51± 2,85	
- < 65 years old	21	70
- ≥ 65 years old	9	30
Sex		
- Male	15	50
- Female	15	50
Education		
- Primary School	4	13.3
- Junior Secondary School	3	10
- Senior Secondary School	17	56.7
- Diploma	1	3.3
- Bachelor Degree	5	16.7
Occupations		
- Housewives	11	36.7
- Entrepreneur	5	16.7
- Government Employees	4	13.3
- Farmer	4	13.3
- Retired	3	10
- Student	2	6.7
- Private Employees	1	3.3
GIDM		
- GIDM	11	36.7
- Not GIDM	19	63.3

Types of tumor subjects in the study were divided into primary brain tumors by 14 subjects (46.7%) and metastatic brain tumors by 16 subjects (53.3%). This can be seen in table 2 below.

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Table 2. Frequency Distribution of Primary Brain Tumor and Metastatic Brain Tumor Patients (n = 30)

Frequency Distribution	n(30)	Percentage
Primary Brain Tumor	14	46.7
Metastatic Brain Tumor	16	53.3

The most metastatic origin in this study were lung cancer by 9 subjects (56.3%) and least of all were cervix cancer, ovarian cancer and sinonasal cancer by 1 subjects for each (6.3%). This can be seen in table 3 below.

Table 3. Frequency Distribution of Metastatic Origin

Frequency Distribution	n(16)	Percentage
Lung Cancer	9	56.3
Breast Cancer	2	12.5
Nasopharynx Cancer	2	12.5
Cervix Cancer	1	6.3
Ovarian Cancer	1	6.3
Sinonasal Cancer	1	6.3

Based on Fisher's test of 30 study samples, it was found that there was no difference in the proportion of age groups for the incidence of GIDM with p value > 0.05. This can be seen in table 4 below.

Table 4. Difference in Age Group Proportion to Incidence Glucocorticoid Induced Diabetes Mellitus

	GIDM	Not GIDM	p	RR
	n(%)	n(%)		
Age ≥ 65 years old	5(55.6)	4(44.4)	0.22	1.94
Age < 65 years old	6(28.6)	15(71.4)		

Based on Eta correlation test of 30 study samples, the results show that there is no association between ages and the incidence of GIDM with p value > 0.05. This can be seen in table 5 below.

Table 5. Association between Ages and Glucocorticoid Induced Diabetes Mellitus

			p
Nominal by Interval	Eta	Ages	0.191
		GIDM	0.755

Discussion

The mean age characteristics of intracranial tumor patients in this study were 51.36 ± 2.85 years. This characteristic of the mean age of intracranial tumor patients is relevant to the previous study conducted by Rambe et al (2013) which mentions the average age of intracranial tumor patients at 51.45 years with an age range of 11-87 years.[11] In the study conducted by Setiawan et al (2015) found that most subjects were in the age group 41-50 years as many as 9 people (52.9%).[4] The incidence rate increases with age, the highest in people over 85 years.[12] Based on age, the older the respondent's age, the higher the risk of getting a tumor. The peak is reached at the age of 35 to 44 years, then slowly the risk will decrease and an increase at age> 65 years.[13]

In this study, sex characteristics of intracranial tumor patients were found to be the same between men and women as many as 15 subjects (50%). In a study conducted by Rambe et al (2013), there were more brain tumor sufferers in men (60.47%) than women (39.26%).[11] Research conducted by Setiawan et al. (2015), there were more brain tumors in women namely 11 subjects (64.7%) compared to 6 subjects (35.3%) for men.[4] The results of the study by Dewi et al (2016) stated that there were more cases of intracranial tumors in women, 37 cases (62.7%) while in men there were 22 cases (37.3%). The ratio of male to female is 1: 2.[14] Aninditha et al (2019) say that women have a higher incidence of CNS tumors than men which may be caused by a high incidence of meningiomas in women. This is thought to be due to the role of sex hormones in women.[15]

In this study the highest level of intracranial tumor patient education was 17 high school subjects (56.7%). This result is relevant to previous research conducted by Setiawan et al (2015) which states that the highest level of education of intracranial tumor patients in his study was SMA, which was 23.5%.[4] In people with higher education, exposure to information about tumor disease will be greater compared to people with low education.[13]

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The occupational characteristics of intracranial tumors in this study were found most frequently were housewives in 11 subjects (36.7%). The results of this study are relevant to previous studies conducted by Rambe et al (2013) which mentioned that most of the work of the research subjects were 26 housewives (34.7%).[11] Research conducted by Setiawan et al (2015) states that the most work in intracranial tumor patients are employees as many as 6 subjects (35.5%).[4] Job status is one aspect related to physical activity. Physical activity is very necessary to maintain health. Physical activity is the movement of limbs which causes energy expenditure which is very important for physical and mental maintenance, as well as maintaining quality of life to stay healthy and fit throughout the day. Physical activity will reduce the risk of colonic cancer, breast cancer and endometrial cancer.[13]

In this study, research subjects who experienced GIDM were 11 subjects (36.7%) and not GIDM were 19 subjects (63.3%). This is consistent with the study of Schultz et al (2017) which states that as many as 22% of intracranial tumor patients given glucocorticoid therapy experience GIDM within the first seven days.[1] Hyperglycemia is reported in 72% of primary brain tumor patients receiving dexamethasone therapy.[6] Steroids cause hyperglycemia both in people with DM and can cause DM in patients without a history of increased glucose levels before. Glucocorticoids can cause hyperglycemia due to insulin resistance and β cell dysfunction.[16]

In this study, the characteristics of intracranial tumor patients which were the most frequent were metastatic brain tumors of 16 patients (53.3%). This is different from the results of the study of Rambe et al (2013) who found 56 primary subjects (74.7%) with primary brain tumors and 19 secondary brain tumors (25.3%).[11] Brain metastasis is a neurological complication of systemic malignancy. The incidence of brain metastases over time increases with the detection of malignancy and the development of cancer management procedures. Metastatic brain tumors occupy the most frequent intracranial tumors, surpassing primary tumors.[15] Metastatic brain tumors account for 25% of all metastatic events. Metastatic brain tumors also account for 20-40% of all adult tumor events.[17] The incidence of metastatic brain tumors is about 10 times more than brain tumors primary in adults. About 30% of adults with systemic tumors will develop into brain metastases.[18]

The largest source of metastasis in this study was 9 lung lungs (56.3%). This is in accordance with the study of Rambe et al (2013) which said that most metastases originated in the lungs by 11 subjects (57.9%).[11] In general, all tumors that are malignant can metastasize to the brain. In adult patients, the primary tumors most often metastasize to the brain are the lung (36-64%), breast (15-25%), and melanoma (5-20%), while about 10-15% of the primary tumor is unknown. Other malignancies can also be metastases to the brain such as the colon, rectum, kidney, prostate, testes, ovaries and sarcoma.[15]

In this study based on statistical analysis of 30 subjects, it was found that there was no difference in the proportion of age groups for the incidence of GIDM with $p > 0.05$. The results of this study differ from previous studies conducted by Katsuyama et al (2015) who conducted research on risk factors for GIDM in patients with kidney disease and rheumatoid disease. Research Katsuyama et al mentioned that research subjects with age > 65 years 2.95 times more at risk of developing GIDM compared to subjects with age < 65 years.[8] Another study conducted by Lee et al (2013) on lymphoma patients who received chemotherapy stated that patients > 60 years old were 3.59 times more at risk for GIDM compared to patients < 60 years old.[19] The difference in the results of this study with previous studies due to differences in research subjects and the length of time of observation. This study was conducted in patients with intracranial tumors with a time of observation of 5 days while the study conducted by Katsuyama et al was conducted in patients with kidney disease and rheumatoid disease with a time of observation of 28 days and research conducted by Lee et al was carried out in lymphoma patients with an observation time of 25 days. In addition, this study found research subjects with <65 years of age totaling 21 people while research subjects with> 65 years of age totaling 9 people. It causes insignificant results in this study. A meta-analysis study conducted by Liu et al (2014) showed an incidence of GIDM of 12% in the elderly population.[10] Katsuyama et al (2015) stated that age is a risk factor for GIDM. This is because glucose tolerance and B cell function have declined in old age.[8]

In this study, based on the statistical analysis of the eta correlation test on 30 subjects, it was found that there was no significant relationship between age and the incidence of GIDM with $p> 0.05$. The results of this study differ from previous studies conducted by Tariq et al (2018) in patients with dermatological disease who received steroid therapy. The results of Tariq et al's study stated that there was a significant relationship between age and the incidence of GIDM ($p <0.05$).[20]

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Katsuyama et al (2015) conducted a study of risk factors for GIDM in patients with kidney disease and rheumatoid disease. The research of Katsuyama et al mentions that age is a risk factor for GIDM. Research subjects aged> 65 years were 2.95 times more at risk of developing GIDM compared to subjects with age <65 years.[8] Another study conducted by Lee et al (2013) on lymphoma patients who received chemotherapy stated that patients> 60 years old were 3.59 times more at risk for GIDM compared to patients <60 years old.[19] The difference in the results of this study with previous studies due to differences in research subjects and the length of time of observation. This study was conducted in intracranial tumor patients with a time of observation of 5 days research conducted by Tariq et al was conducted in patients with dermatological conditions with a time of observation of 6 months, research conducted by Katsuyama et al conducted on patients with kidney disease and rheumatoid disease with a time of observation of 28 days and research conducted by Lee et al conducted on lymphoma patients with observation time 25 days. In addition, this study found research subjects with <65 years of age totaling 21 people while research subjects with> 65 years of age totaling 9 people. It causes insignificant results in this study.

Kim et al (2011) conducted a study of 231 patients who received steroid therapy and concluded that old age was the only risk factor for GIDM.[9] In brain tumor patients, glucocorticoids are the main therapy for treating peritumoral edema.[1] Corticosteroids have been widely used in tumor therapy and are useful in brain tumor patients with significant peritumoral edema accompanied by neurological deficits.[2] Dexamethasone decreases VEGF expression through activation of glucocorticoid receptors thereby improving brain blood barrier barrier dysfunction.[4]

The use of steroids has side effects, one of which is hyperglycemia. Steroids cause hyperglycemia both in people with DM and can cause DM in patients without a history of a previous increase in glucose levels or so-called GIDM.[5] Glucocorticoids can cause hyperglycemia due to insulin resistance and b cell dysfunction.[16] Katsuyama et al (2015) say that old age is a risk factor for GIDM.[8] This is because glucose tolerance and B cell function have declined in old age. Glucose tolerance decreases progressively with age. With aging, B cell function decreases and basal insulin secretion level also decreases.[9] B cells are a place of synthesis and secretion of insulin. With a decrease in b cell function, it will reduce insulin synthesis and secretion (Banjarnahor and Wangko, 2012).

Conclusion

There is no difference in the proportion of the age group to the incidence of GIDM and there is no significant association between age and the incidence of GIDM.

Suggestion

Further research can be done with a longer observation time. The use of diagnostic tests with tissue biopsy needs to be done in order to get better results.

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