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Profile of Coagulation Marker and The Influence Factors in Central Nervous System Tumor

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ABSTRACT

Brain tumors have the highest percentage of thrombosis compared to other types of malignancies. Hypercoagulation is a risk for thromboembolic events in patients with malignancy. Hypercoagulation conditions are frequently found in patients with malignancy arising from the aptitude of tumor cells to activate the coagulation system. This condition can be detected through coagulation markers in the blood. This marker is PT, APTT, INR, Fibrinogen and D-Dimer. This research is a descriptive analytic study using secondary data from medical records of patients with central nervous system (CNS) tumors. The inclusion criteria were CNS tumor patients > 18 years old and had been diagnosed with CNS tumor. Coagulation markers are recorded based on the results of the initial laboratory examination upon entering the hospital, consisting of D-Dimer, PT, APTT, Fibrinogen, INR. There were 124 research subjects, consisting of 60 men and 64 women. Most research subjects are in the age range of 40-49 years (54.8%). Hypercoagulation conditions were found in 92.74% of study subjects. The most common accompanying condition was hypertension (22.6%). There were no significant differences in the hypercoagulable conditions in groups with and without accompanying conditions. Hypercoagulation was found in most research subjects. There are no factors that influence the hypercoagulation condition in this study.

Keywords: hypercoagulation, accompanying conditions, coagulation markers, CNS tumors

ABSTRAK

Tumor otak memiliki presentase kejadian trombosis paling tinggi dibandingkan dengan tipe keganasan yang lain. Hiperkoagulasi merupakan suatu resiko untuk kejadian tromboemboli pada penderita dengan keganasan. Kondisi Hiperkoagulasi sering ditemukan pada penderita keganasan timbul karena adanya kemampuan sel-sel tumor untuk mengaktivasi sistem koagulasi. Kondisi hiperkoagulasi ini dapat dideteksi melalui petanda koagulasi pada darah. Petanda koagulasi ini dapat berupa PT, APTT, INR, Fibrinogen dan D-Dimer. Penelitian ini merupakan penelitian deskriptif analitik dengan menggunakan data sekunder rekam medis penderita tumor susunan saraf pusat (SSP). Kriteria inklusi adalah penderita tumor SSP usia > 18 tahun dan telah ditegakkan diagnosa tumor SSP. Penanda koagulasi dicatat berdasarkan hasil pemeriksaan laboratorium awal saat masuk RS, terdiri dari D-Dimer, PT, APTT, Fibrinogen, INR. Didapatkan 124 subjek penelitian, yang terdiri dari 60 laki-laki dan 64 perempuan. Sebagian besar subjek penelitian berada pada rentang usia 40-49 tahun (54,8%). Kondisi hiperkoagulasi didapatkan pada 92,74% subjek penelitian. Kondisi penyerta yang paling sering dijumpai adalah hipertensi (22,6%). Tidak didapatkan perbedaan bermakna terhadap kondisi hiperkoagulasi pada kelompok dengan dan tanpa kondisi penyerta. Hiperkoagulasi dijumpai pada sebagian besar subjek penelitian. Tidak didapatkan faktor yang mempengaruhi kondisi hiperkoagulasi pada penelitian ini.

Kata kunci: hiperkoagulasi, kondisi penyerta, petanda koagulasi, tumor SSP

1. Introduction

The World Health Organization (WHO) establishes cancer as a global health problem. Data from the National Cancer Institute in 2010-2014 shows that new cases of CNS cancer reach 6.4 / 100,000 men and women per year.[1] In Indonesia the incidence of central nervous system tumors is increasing each day. With an increase in the incidence of these tumors there is also an increase in the complications they cause.

It is well known that tumors are associated with thrombosis risk. Brain tumors have the highest percentage of thrombosis events compared to other types of malignancies, which is 26%. [2] Hypercoagulation is one of the risk factor for thromboembolic events in patients with malignancy. Hypercoagulation in malignancy was first reported in 1865 by Armand Trousseau, who first described the clinical link between thromboembolic disease and malignancy.[3]

Hypercoagulation conditions are often found in patients with malignancy arising from the aptitude of tumor cells to activate the coagulation system. The state of hypercoagulation reflects the interaction of different mechanisms involving the activation of various hemostatic physiology components. Tumor cells interact with all parts of the hemostatic physiology system. Tumor cells can directly activate the coagulation cascade by producing their own procoagulant factors or stimulating the prothrombotic nature of other blood cell components.[4] This hypercoagulable condition can be detected through coagulation markers in the blood. This coagulation marker can be PT, APTT, INR, Fibrinogen and D-Dimer.[5] This study aims to determine the profile of coagulation markers and the factors that influence it in patients with central nervous system tumors.

2. Methods

This research is an analytical descriptive study using secondary data from medical records of patients with central nervous system tumors from January 2017 to December 2018 at RSUP Mohammad Hoesin Palembang. The inclusion criteria were CNS tumor patients > 18 years old and diagnosis was made based on histopathological features. In the case of metastatic tumors, the diagnosis is based on imaging in the form of a CT scan or MRI. Subjects with a history of or currently taking antiplatelet or anticoagulant were excluded in this study. Coagulation markers are recorded based on the results of the initial laboratory examination upon entering the hospital, consisting of D-Dimer, PT, APTT, Fibrinogen, INR. Hypercoagulation is defined if there is an increase above the normal value of one or more of the coagulation markers. Diseases associated with hypercoagulation were also noted. Data analysis using SPSS 24 for Windows.

3. Results

In this study there were 124 research subjects. The mean age of patients with CNS tumors was 47.97 ± 12.63 years old. Based on age category, most patients were aged 40-59 years old (54.8%), with the proportion not much different between women (51.6%) and men (48.4%). As many as 59.7% of study subjects had accompanying conditions, with the most common accompanying condition being hypertension (22.6%). Neurological deficits were found in almost all study subjects (99.2%). Based on tumor characteristics, the proportion of metastatic tumors was higher than primary tumors (63.7% and 36.3%) with a higher number of multiple tumor lesions (59.7%).

By location, brain tumors are more common than spinal cord tumors (89.5% and 10.5%). Hypercoagulation conditions were found in 92.74% of research subjects. There was no significant difference in the occurrence of hypercoagulation in groups with accompanying conditions and without accompanying conditions (p = 0.483). The analysis can be seen in table 1.

Table 1. Clinical characteristics of study subjects (n = 124)

Characteristics	Total Frequency n (%)	Hypercoagulation n (%)	No Hypercoagulation n (%)	p value
Age (Mean±SD)	47,97±12,63	48,58±12,38	40,22±13,98	0,056[a]
Age Category				
<40 years old	32(25,8)	27(84,4)	5(15,6)	0,072[b]
40-59 years old	68(54,8)	65(95,6)	3(4,4)	
≥60 years old	24(19,4)	23(95,8)	1(4,2)	
Gender				
Male	60(48,4)	56(93,3)	4(6,7)	1,000[c]
Female	64(51,6)	59(92,2)	5(7,8)	
With Accompanying Conditions				
Yes	74(59,7)	70(94,6)	4(5,4)	0,483[c]
No	50(40,3)	45(90,0)	5(10,0)	
- **Hypertension**				
Yes	28(22,6)	27(96,4)	1(3,6)	0,682[c]
No	96(77,4)	88(91,7)	8(8,3)	
- **Diabetes Melitus**				
Yes	5(4,0)	4(80,0)	1(20,0)	0,318[c]
Not	119(96,0)	111(93,3)	8(6,7)	
- **History of TIA/Stroke**				
Ya	8(6,5)	8(100,0)	0(0,0)	1,000[c]
Tidak	116(93,5)	107(92,2)	9(7,8)	
- **Atrial Fibrillation**				
Yes	3(2,4)	3(100,0)	0(0,0)	1,000[c]
No	121(97,6)	112(92,6)	9(7,4)	
- **Smoking**				
Yes	6(4,8)	6(100,0)	0(0,0)	1,000[c]
No	118(95,2)	109(92,4)	9(7,6)	
- **Dyslipidemia**				
Yes	1(0,8)	0(0,0)	1(100,0)	0,073[c]
No	123(99,2)	115(93,5)	8(6,5)	
- **Infection**				
Yes	24(19,4)	24(100,0)	0(0,0)	0,204[c]
No	100(80,6)	91(91,0)	9(9,0)	

Neurological deficit				
Yes	123(99,2)	115(93,5)	8(6,5)	0,073[c]
No	1(0,8)	0(0,0)	1(100,0)	
Tumor Type				
Primary	45(36,3)	42(93,3)	3(6,7)	1,000[c]
Metastasis	79(63,7)	73(92,4)	6(7,6)	
Amount of Tumors				
Single	50(40,3)	47(94,0)	3(6,0)	0,739[c]
Multiple	74(59,7)	68(91,9)	6(8,1)	
Tumor Location				
Brain	111(89,5)	104(93,7)	7(6,3)	0,239[c]
Spinal Medulla	13(10,5)	11(84,6)	2(15,4)	

[a]*Independent T Test,* [b]*Mann Whitney,* [c]*Fischer Exact Test*

In the group of subjects with hypercoagulation, it was found that most of the subjects (60.87%) had aaccompanying conditions, with the most age group being 40-59 years old. There was a significant difference in the incidence of hypercoagulation in groups with and without accompanying conditions (p = 0.029). The analysis can be seen in table 2.

Table 2. Distribution of Proportions of Hypercoagulation Patients Based on Accompanying Conditions (n = 115)

Characteristics	With Accompanying Conditions n (%)	Without Accompanying Conditions n (%)	P Value
Age (Mean±SD)	49,48±13,42	47,17±10,57	0,307[a]
Age Category			
<40 years old	17(63,0)	10(37,0)	0,213[b]
40-59 years old	34(52,3)	31(47,7)	
≥60 years old	19(82,6)	4(17,4)	
Gender			
Male	37(66,1)	19(33,9)	0,265[c]
Female	33(55,9)	26(44,1)	
Tumor Type			
Primary	23(54,8)	19(45,2)	0,309[c]
Metastasis	47(64,4)	26(35,6)	
Amount of Tumor			
Single	23(48,9)	24(51,1)	0,029[c]
Multiple	47(69,1)	21(30,9)	

Tumor Location			
Brain	63(60,6)	41(39,4)	1,000[d]
Spinal Medulla	7(63,6)	4(36,4)	
Total Neurological Deficits			
1 deficit	14(46,7)	16(53,3)	0,064[c]
2 deficits	27(57,4)	20(42,6)	0,532[c]
3 deficits	24(72,7)	9(27,3)	0,098[c]
4 deficits	5(100,0)	0(0,0)	0,155[d]

[a]*Independent T Test,* [b]*Mann Whitney,* [c]*Pearson Chi Square,* [d]*Fischer Exact Test*

In the group of subjects who did not have concomitant conditions, statistical analysis showed a significant difference in the age ratio between patients with hypercoagulation (46.03 ± 10.21) and without hypercoagulation (35.60 ± 10.14) ($p < 0.05$). While in the other categories include gender, type of tumor, amount of tumor and tumor location, there were no significant differences in hypercoagulable conditions ($p > 0.05$). The analysis is shown in table 3.

Table 3. Distribution of Proportion of Patients without Accompanying Conditions with Hypercoagulation (n = 50)

Characteristics without Accompanying Conditions (n = 50)	**Hypercoagulation n (%)**	**Without Hypercoagulation n (%)**	**P Value**
Age (Mean±SD)	47,17±10,57	35,40±9,99	0,022[a]
Age Category			
<40 years old	10(76,9)	3(23,1)	0,140[b]
40-59 years old	31(93,9)	2(6,1)	
≥60 years old	4(100,0)	0(0,0)	
Gender			
Male	19(90,5)	2(9,5)	1,000[c]
Female	26(89,7)	3(10,3)	
Tumor Type			
Primary	19(86,4)	3(13,6)	0,643[c]
Metastasis	26(92,9)	2(7,1)	
Amount of Tumor			
Single	24(88,9)	3(11,1)	1,000[c]
Multiple	21(91,3)	2(8,7)	
Tumor Location			
Brain	41(91,1)	4(8,9)	0,423[c]
Spinal Medulla	4(80,0)	1(20,0)	
Total Neurological Deficits			
1 deficit	16(88,9)	2(11,1)	1,000[c]
2 deficits	20(87,0)	3(13,0)	0,651[c]
3 deficits	9(100,0)	0(0,0)	0,570[c]

[a]*Independent T Test,* [b]*Mann Whitney,* [c]*Fischer Exact Test*

4. Discussion

An increased risk of thrombosis is associated with changes in blood flow, injury to the vascular endothelium and changes in blood constitution known as virchow's triad. It is well known that thrombosis and malignancy are related by several complex pathophysiological mechanisms.[5,6,7,8,]

Tumor cells can activate the blood coagulation system through several mechanisms such as the production of procoagulant factors, fibrinolytic activity, proagregation, release of proinflammatory and proangiogenic cytokines and direct interaction with vascular vessels and blood cells through adhesion molecules. Procoagulant factors produced by tumor cells are Tissue Factor (TF) and Cancer Procoagulant (CP). In addition, tumor cells also produce and secrete a number of normal proinflammatory cytokines in vascular endothelium, for example TNF-a and IL-1b. [9,10,11,12]

It is known that malignancy itself is one of the conditions underlying hypercoagulation. Age and sex are known to affect hypercoagulable conditions. Old age cause an increased risk of hypercoagulation. In America the incidence of hypercoagulation that causes symptomatic thromboembolism is generally passed down higher in men than in women.[4.13] In addition, several accompanying conditions that affect hypercoagulation can sometimes be found together in malignant sufferers. These accompanying conditions include smoking, immobilization, thrombocytosis, pregnancy, metabolic diseases such as hypertension, DM, atrial fibrillation and infection. With this accompanying condition, it certainly increases the risk of hypercoagulation in patients with CNS tumors.

The incidence of hypercoagulation in malignancies varies depending on the type of malignancy itself. Brain tumor is one type of malignancy that has a high incidence of hypercoagulation. In this study hypercoagulation was found in 92.74% of subjects, where metastatic tumors had higher rates than primary tumors. This is related to the rate of metastasis at this time is much higher compared to primary CNS tumors. Old age group is the largest proportion of CNS tumor events. These results are consistent with previous studies by Eppy et al, who found the age group of 40-59 years.[14] Research by Goldschmidt et al, also showed that the age of most brain tumor sufferers was > 50 years (71.4%) .[15] Increased incidence of brain tumors in old age related to the length of exposure needed by a cell to become malignant or decrease the body's defense system resulting in a decrease in the immune system in protection against disease. Old age is associated with hypercoagulation which causes venous thromboembolism (VTE). Old age is associated with increased plasma levels of many blood coagulation proteins and disruption of the fibrinolysis process.[16]

In this study, there was no significant difference in the presence or absence of accompanying conditions with hypercoagulation while not hypercoagulation. This is related to the high incidence of hypercoagulation in this study (92.74%). This result is different from previous studies by Eppy et al., which showed a large percentage of accompanying conditions in patients with hypercoagulation (69.6%) compared to non-hypercoagulation (30.4%).[14] Accompanying conditions are associated with an increased risk of cancer-related thrombosis. Co-morbid conditions such as kidney failure, respiratory disease, heart disease, obesity and acute infections are associated with an increased risk of VTE in cancer patients.[17]

Smoking as a accompanying condition was found in 4.8% of patients with CNS tumors, no significant differences in smoking factors were found between hypercoagulable and non-hypercoagulable patients. This is in line with the research of Zhang et al., Which found no significant differences in smoking factors between VTE and non-VTE patients.[18] Cigarettes are known to have an important role in the pathogenesis of VTE, through elevation in fibrinogen levels. Although this mechanism is unclear and there are many factors that can cause an increase in fibrinogen levels, several studies have reported an increase in fibrinogen levels in active smokers.[19]

Tumor factor itself can not be determined whether the type and number of tumor lesions that affect the condition of hypercoagulation. In the study the number of lesions was significant for the incidence of hypercoagulation. A similar finding was found in research conducted by Suega and colleagues who explained that the number of tumor lesions did not have a significant correlation between coagulation markers and the type of malignancy that classified primary (single) and secondary (multiple) tumors. The research of Setiawan et al. also received similar results. Research by Suega et al. shows that primary tumor classification and metastasis have higher preoperative D-dimer levels in patients with larger and multiple tumor volumes.[7,20]

5. Conclusion

In this study showed that the incidence of hypercoagulation in patients with CNS tumors is very high, where there is no significant difference in groups who have accompanying conditions and without accompanying conditions. There are no factors that significantly influence the incidence of hypercoagulation in patients with CNS tumors. This research itself is an observational study based on the results of medical records where there is a possibility of data bias that affects the results of the analysis.

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