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Association Between Cigarette Smoking And Cognitive Function In Stroke Patients Of Siloam Lippo Karawaci Hospital.

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Abstract

Stroke is a cerebrovascular disease, causing deterioration of brain function as a result of cerebral blood flow disruption. Stroke is the third leading cause of death in the world and is considered an important cause of long-term disability and cognitive impairment. Risk factors of stroke are further divided into unmodifiable risk factors and modifiable risk factors, with one of the most common modifiable risk factors of stroke, is cigarette smoking. Besides being one of the risk factors that cause stroke, cigarette smoking is believed to have a role in cognitive impairment. This study aims to obtain information regarding the association between cigarette smoking and cognitive function in stroke patients of Siloam Lippo Karawaci Hospital. This research is an unpaired comparative analytical study with a cross-sectional design. Data sampling was taken by consecutive sampling on 56 stroke patients of Siloam Lippo Karawaci Hospital. Cognitive function was made based on the Montreal Cognitive Assessment version Indonesia (MoCA-INA). All data were analyzed by Chi-Square test using SPSS version 25 and the result is considered significant if the p-value < 0,05. From the result of this study. There is a significant association between cigarette smoking and cognitive function (p-value 0,004 and OR 5,343).

Introduction

According to the World Health Organization (WHO), an estimated 15 million people in the world suffer from strokes each year and about 5 million ends up dying with long-term disabilities.[1] WHO also states that there are 15 million people who suffer a stroke every 10 years between the ages of 55 and 85 years.[1] The increase in the things that happen to strokes. The incidence of stroke doubles every 10 years after age 45.[2] In Indonesia, data from the Basic Health Research (Riskesdas) by the Indonesian Ministry of Health (Kemenkes) states that the main cause of death for all ages is stroke (15.4%) followed by tuberculosis and hypertension.[2] WHO also classifies risk factors for stroke incidence, namely non-modifiable and modifiable risk factors. One of the most frequent and underserved risk factors for stroke is smoking. In Indonesia, according to data from the Global Adult Tobacco Survey (GATS), There are 58 million male active smokers and 3.8 million female active smokers with around 85.4% of the population has been exposed to cigarettes in 2015.[3] Data from GATS can be concluded in a period of 4 years, namely from 2011-2015 there is an increase in the number of smokers by 4 million people.[4,3] Smoking becomes main contributor to health problems in Indonesia, although 4 out of 5 people (86%) active smokers in Indonesia know that smoking can causeserious disease with the lowest knowledge of stroke incidence, namely; 40%.[4]

In most people, the incidence of stroke is closely related to smoking habits. Smoking is one of the many risk factors for stroke development with damage to blood vessels and contributing to the formation of atherosclerosis or hardening of the arteries.

In 2015, WHO states tobacco smokers have reached 1.3 billion worldwide with 6 million deaths due to cigarette use.[5]

According to several hypotheses, smoking has been linked as a risk factor for cognitive decline. Substances in cigarettes can impair cognitive function by several mechanisms such as the effects of oxidative stress in the brain cells.[6] However, the extent to which smoking increases the risk of declined cognitive function remains unclear.[7] Study by Dobson et al with the title *The Long Term of Smoking Contributes to Cognitive Decline* concludes that smokers over a long period of time contributes to cognitive decline over time aging, which occurs at the peak of the age of 60 years.[8] Research has been done on the relationship between smoking and cognitive function in stroke patients conducted by Ekamala Putri Almi with the title "The Relationship of Smoking Behavior With Impaired Cognitive Function In Ischemic Stroke Patients" found significant results between the two variables.

Materials And Methods

This study used an unpaired categorical analytic study type with a cross-sectional study design. Sampling was based on consecutive sampling, namely the selection of the sample was based on the inclusion and exclusion criteria of the study. The subjects were patients at Siloam Lippo Karawaci Hospital who had previously diagnosed with a stroke by a neurologist. The diagnosis of stroke that are included in this study are both ischemic and hemorrhagic stroke. The inclusion criteria were patients who had been diagnosed with a stroke by a neurologist and were over 45 years old. Exclusion criteria were patients who had a history of dementia and were illiterate. The ethical approval of this study was obtained from The faculty of medicine of Universitas Pelita Harapan with license number (rev)125/K LKJ/ETIK/IV/2019.

Data collection was carried out by direct interviews with patients using the Indonesian version of the Montreal Cognitive Assessment (MoCA-INA) questionnaire after the subjects filled out the consent form to participate in the study. Smoking is obtained based on the patient's history. The MoCA examination includes orientation, short-term memory, executive function, language, abstraction, animal naming, attention, and clock-drawing test. The maximum score of the MoCA-INA is 30, with a total score of 26 to 30 considered normal cognitive function, below 26 are considered poor cognitive, and with the score of below 19 are considered dementia.[9]

Result

The sample obtained in this research are 56 patients that were previously diagnosed with stroke by neurologist in Siloam Hospitals Lippo Village Karawaci. The distribution of respondents for the results of cognitive function with the use of MoCA-INA, from a total of 56 respondents obtained from the interviews in this study, there were 23 (41.1%) respondents who had more than 12 years of education, and 33 respondents (58.9%) who have less than 12 years of proper education. In terms of occupation of the respondents, there were 31 (55,4%) who were unemployed, includes housewives, 7 respondents who are an employee, 14 respondents are an entrepreneur, and 4 respondents with different types of occupations. 27 respondents (48.2%) who got poor MoCA-INA results and 29 respondents (51.8%) who got good MoCA-INA results. The distribution of respondents based on demographic characteristics can be seen in Table 1.

Table 1. Demographic Characteristics

Characteristics	Population N	Percentage (%)
Gender		
Male	31	55,4
Female	25	44,6
Age (year)		
45-64	44	78,6
> 65	12	21,4
Stroke Type		
Ischemic	39	69,6
Hemorrhagic	17	30,4
Hypertension		
Yes	39	69,6
No	17	30,4
Diabetes Mellitus		
Yes	26	46,4
No	30	53,6
Cholesterol		
Yes	23	41,1
No	33	58,9
Metabolic Syndrome		
Yes	5	8,9
No	51	91,1

Based on the results of the cross-tabulation that have been carried out in Table 2, overall there are 24 samples (42.9%) who have a history of smoking with 17 samples (70.8%) getting poor MoCA-INA results and 7 samples (29.2%) get good MoCA-INA results. There were also 32 samples (57.1%) who did not have a history of smoking, with 10 samples (31.3%) getting poor MoCA-INA results and 22 (68.8%) getting good MoCA-INA results.

Table 2. Cross-tabulation and Chi-Square Test Results Relationship Between Cigarette Smoking and Cognitive Function

	MoCA-INA		Total N (%)	P Value	OR (95% CI)
	Bad n (%)	**Good n (%)**			
Cigarette Smoker	17 (70,8)	7 (29,2)	24 (42,9)		
Non Smoker	10 (31,3)	22 (68,8)	32 (57,1)	p = 0,004	5,343(1,684– 16,955)
Total	34 (60,7)	22 (39,3)	56 (100)		

The results of data analysis using the Chi-Square test found the p-value is 0.004. The relationship obtained is also supported by an Odds Ratio of 5.343 and 95% CI = 1.684 - 16,955.

Bivariate Analysis Results

Bivariate analysis was carried out on other variables in this study to see if there was a relationship with cognitive function or the results of the MoCA-INA. Data analysis was performed statistically with the Chi-Square test to obtain the p-value through the SPSS program. From the results obtained (Table 3), several significant variables have a relationship with cognitive function. These variables include gender (p-value = 0.027), smoking (p-value = 0.004), type of stroke (p-value = 0.027). Through this analysis, it was found that there was no significant relationship between age and cognitive function using the MoCA-INA, which was found to be p-value = 0.573.

Table 3. Bivariate Analysis of Variables Associated with Cognitive Function

Variables	MoCA-INA Poor n (%)	Good n (%)	*P value*	OR
Gender				
Male	19 (61,3)	12 (38,7)	0,027	0,297
Female	8 (32,0)	17 (68,0)		
Education				
> 12 years	9 (60,9)	14 (39,1)	0,194	1.867
< 12 years	18 (54,5)	15 (45,5)		
Age (years)				
45-64	21 (47,7)	23 (52,3)	0,573	1.095
> 65	6 (50,0)	6 (50,0)		
Hypertension				
Yes	19 (48,7)	20 (51,3)	0,570	1.069
No	8 (47,1)	9 (52,9)		
Diabetes Mellitus				
Yes	9 (34,6)	17 (65,4)	0,240	0,59
No	18 (60,0)	12 (40,0)		
Metabolic Syndrome				
Yes	2 (40,0)	3(60,0)	0,535	0,693
No	25 (49,0)	26 (51,0)		
Dyslipidemia				
Yes	13 (56,5)	10 (43,5)	0,222	1,764
No	14 (42,5)	19 (57,6)		
Cigarette Smoking				
Yes	17 (70,8)	7 (29,2)	0,004	5,343
No	10 (31,3)	22 (68,8)		
Stroke Types				
Ischemic	15 (38,5)	24 (61,5)	0,027	3.840
Hemorrhagic	12 (70,6)	5 (29,4)		

The results of the bivariate analysis above will be carried out in the multivariate analysis, namely, variables that meet the requirements of the multivariate analysis p-value = <0.25 will be continued for multivariate logistic regression analysis. From the results of the bivariate analysis, the results of p-value <0.25 were gender, diabetes mellitus, smoking, and type of stroke. The multivariate analysis are described in Table 3.

Variables	*P Value*	*Odds Ratio*	95% C.I	
			Lower	Upper
Gender	0.435	0.530	0,107	2.614
Cigarette Smoking	0.165	3.017	0.635	14.328
Stroke Type	0.440	1.772	0.415	7.565
Diabetes Mellitus	0.073	0.313	0.088	1.112

Table 4. Multivariate Regression Logistic Analysis

Discussion

From a total of 56 study respondents, 27 patients had decreased or poor cognitive function and 29 had a cognitive function that tended to be normal or good. The results of statistical tests using Chi-Square analysis show a significance value of p-value 0.004, which means that if the p-value is less than 0.05, it indicates that smoking has a significant relationship to cognitive function. The relationship obtained is also supported by an Odds Ratio of 5.343 and 95% CI = 1.684 - 16,955, which means that cognitive function deteriorates 5.343 times more in stroke patients who smoke compared to other stroke patients who do not smoke. This is by what was stated by Sabia (2012), namely the study involved a sample of 5099 respondents with male gender and 2137 others were women with significant results obtained with a p-value of 0.03, where the cognitive average tended to decrease in the male smoker.10Like the research above, this study also concluded that cognitive decline was supported by long-term smoking behavior for at least 10 years. This study found that male respondents who smoked for 10 years had a 10-year decline in cognitive function.

After analyzing the four variables from the bivariate model to the multivariate regression analysis, it was found that the four variables, namely gender, smoking, stroke type, and diabetes mellitus independently did not affect cognitive function. This is because the results of multivariate logistic regression analysis obtained a p value> 0.05, which means there is no significant relationship independently.

The results of this study are in accordance with previous studies that have been carried out by Ekamala Putri Almi where the results found indicate the presence of a significant relationship between smoking and cognitive function in patients stroke where the result is smoking decreases cognitive function. Research concluded that the free radicals contained in cigarettes can interfere with the transport of oxygen to the brain and also increasing the number of free radicals in the brain circulation can cause damage and death of brain nerve cells.[11]

One study that were conducted in China by Zhou in 2003 on the relationship between smoking and cognitive decline in the elderly, where in the study includes 3012 elderly,the p value found was 0.027. But this study cannot conclude whether the effect is the

frequency, history, and types of cigarettes used.[7]

In contrast to a 10-year cohort study in Taiwan, which found that smokers tend to reduce the risk of cognitive decline compared to non-smokers and this is concluded because the nicotine in the smoking can improve cognitive function.[12]The results of this study are inversely proportional to the research conducted by Marchadinda Inggriani Suprapto with the title "The Relationship of Smoking History" With Cognitive Disorders in Stroke Patients" where no results were found which is significant between the two variables, namely the result of p value of 0.408. Whereas the conclusion of that study was that many of the samples had stopped smoking 5-10 years.

This study has several weaknesses, among others, the distribution of this study is not normal. Also, the research method used in this study unable to assess the causal relationship between the variables that exist with cognitive function.

This study also has a weakness in the sample included where the sample is only 56 respondents and only carried out at a certain time, where the results obtained not necessarily able to describe the same conditions with a different population and place. In addition, this study has respondents with a variable timing of stroke attacks and frequency. Therefore, it is expected that the effects of smoking such as frequency, type, and history or active smokers and also the timing of stroke can be measured by means or tools that are more specific and sensitive in the future research. Other factor related to cognitive decline not that is not being evaluated in this study such as diabetes also need a further research in terms of the correlation with smoking and cognitive function.

Because this study is limited in Siloam Hospitals Lippo Village, it is hoped that the results of this study can contribute to providing data of the correlation between cigarette smoking and cognitive function in stroke patients and as a motivation so this issue will become a concern in other hospitals in Indonesia. This study also hoped that it can help stroke patients to stop smoking, and for active smokers to stop cigarette smoking in terms of the occurrence of an increase number of individuals with cognitive decline.

Conclusion

Based on the results of research regarding the relationship between smoking and cognitive function in stroke patients at Siloam Lippo Karawaci Hospital, it can be concluded that there is a relationship between smoking and cognitive function in stroke patients at Siloam Lippo Karawaci Hospital which can be concluded from the p-value of 0.004. Of the 56 samples who participated in this study, there were 24 samples (42.9%) with a history of smoking and 27 samples (48.2%) with poor cognitive function. Then there is no relationship between gender, stroke type, age, education. Further study needed in terms of evaluating other factors related with stroke and cognitive function with a prospective cohort study to confirm the results.

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Association Between Quality Of Sleep With Primary Headache In Siloam Hospital Karawaci

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Abstract

Primary headache is a the most common neurological complaint, and experienced by almost everyone throughout life. The most common type of primary headache is TTH (Tension Type Headache) and Migraine. Quality of sleep is associated with life satisfaction and data shows that one third of adults are affected by poor sleep. Many studies have mentioned that there is a relationship between quality of sleep and primary headache, but no study have ever been conducted in Siloam Hospital Karawaci. We did a case control study in Siloam Hospital Karawaci using purposive sampling, with a total of 50 patients as the subjects. Data were collected using PSQI questionnaire and DASS 42 between January 2019 – March 2019. It was found that there was a significant relationship between sleep quality and primary headache (p= <0,001).

Introduction

Primary headaches were disorders that encompasses a wide group of neurological disorders causing recurrent or persistent headaches for no apparent reason. The most common type of primary headache is tension-type headaches (TTH) and migraines.[1] People who experience sleep disorders usually have poor sleep quality which can cause other health problems.[2] Previous studies found a higher prevalence of poor sleep quality in patients with migraines compared to people without migraines.[3] In individuals with chronic TTH, stress and sleep disturbances are the most common causes.[4] Houle, et al. found that individuals who are sleep deprived for two consecutive days are at risk for experiencing headaches compared to individuals with adequate sleep.[5]
Shorter sleep duration is associated with more severe headaches.[5] Also study shows 48 - 74% of patients with migraines and 26 - 71% of patients with TTH show lack of sleep as a triggering factor for headache attacks.[6] Almost all adults have experienced primary headaches. Several previous studies have shown the presence of a relationship between poor sleep quality and the occurrence of primary headache, especially migraine-type headache and TTH.

Methods

This research is a quantitative analytic study. The subjects are Siloam Karawaci Hospital patients aged 20-50 years old who had been diagnosed with migraine or TTH in January-March 2019 by a neurologist based on the diagnostic criteria International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-III beta). Exclusion criteria are patients who are diagnosed with a previous secondary headache or had a history of mild to severe head trauma at least 3 months previously.
Data collection was conducted by direct interview using a Pittsburgh Sleep Quality

Index (PSQI and Depression, Anxiety and Stress Scales (DASS-42) questionnaire. Quality of sleep was assessed through the PSQI questionnaire which distinguished good sleep quality (PSQI ≤ 6) and poor sleep quality (PSQI > 6). The DASS-42 questionnaire can measure three types of emotional states, which are depression, anxiety, and stress in a person. Depression was divided into non-depression (DASS score for depression ≤9) and depression group (DASS score for depression >9), anxiety was divided into non - anxiety (DASS score for anxiety ≤7) and anxiety group (DASS score for anxiety >7) and stress was divided into non-stress (DASS score for stress ≤14) and stress group (DASS score for stress >14).

Based on frequency, Migraine and TTH can be divided into three group such as mild (<1 day/month), moderate (1-14 days/month), and severe (≥14 days/month). Descriptive analysis is used to study the characteristics of the respondent subject that include the average age, gender, and occupation. Chi Square bivariate analysis was conducted to determine the relation between quality of sleep and primary headaches, while also looking for other variables associates with primary headaches such as depression, anxiety, and stress. Fisher's Exact test was performed to analyze the relationship between sleep quality and primary headache frequency because it did not meet the requirements for Chi Square.

Result

A total of 50 respondents who meet the inclusion criteria were collected and the characteristic as shown in Table 1. Out of 50 respondents, 25 respondents have primary headaches and 25 other respondents are control group that do not have primary headaches.

Table 1. **Demographic characteristic of the subjects**

Characteristic	Primary Headache, n(%) (n=25)	Control Group, n(%) (n=25)	Total Population, n(%) (n= 50)
Mean Age ± SD, years	37.92 ± 9.01	31.88 ± 9.17	34.90 ± 9.50
Gender			
Man	8 (32)	9 (36)	17 (34)
Woman	17 (68)	16 (64)	33 (66)
Job			
Housewife	10 (40)	7 (28)	17 (34)
Private Employees	6 (24)	7 (28)	13 (26)
Government Employees	2 (8)	2 (8)	4 (8)
Merchant	3 (12)	2 (8)	5 (10)
Student	1 (4)	4 (16)	5 (10)
Barista	0	2 (8)	2 (4)
Security	0	1 (4)	1 (2)
Teacher	1 (4)	0	1 (2)
Taxi bike	1 (4)	0	1 (2)
Builder	1 (4)	0	1 (2)

Based on tests conducted by bivariate analysis method there are two variables that have a significant association with primary headaches. These variables are quality of sleep (P = <0.001) and depression (P = 0.001). The results of the bivariate analysis are shown in Table 2.

Table 2. **Correlation between Quality of Sleep, Depression, Anxiety, Stress and Primary Headache**

Variable	Primary Headache , n(%) (n=25)	Control Group , n(%) (n=25)	*P value*	OR
Quality of Sleep				
Good	3 (12)	23 (92)	<0,001*	84,333
Poor	22 (88)	2 (8)		
Depression				
Yes	14 (56)	2 (8)	0,001*	14,636
No	11 44)	23 (92)		
Anxiety				
Yes	16 (64)	9 (36)	0,090	3,16
No	9 (36)	16 (64)		
Stress				
Yes	12 (48)	6 (24)	0,141	2,923
No	13 (53)	19 (76)		

In addition to analyzing quality of sleep association with primary headache, another analysis was also conducted to determine the sleep quality's association with the frequency of primary headache. The analysis included frequency of the overall primary headaches (TTH and migraine), frequency of TTH, and frequency of migraine. This analysis was performed by

combining mild and moderate frequencies into one group, followed by severe frequencies and its association with quality of sleep (Table 3, Table 4, Table 5).

Table 3. **Correlation Between Quality of Sleep and Primary Headache Frequency**

Variable	Primary Headache Frequency, n (%)		*P Value*	OR
	Mild-Moderate	Severe		
Quality of Sleep				
Good	7 (50)	2 (18,2)	0,208	4,5
Poor	7 (50)	9 (81,8)		

Table 4. **Correlation Between Quality of Sleep and TTH Frequency**

Variable	TTH Frequency, n (%)		*P Value*	OR
	Mild-Moderate	Severe		
Quality of Sleep				
Good	4 (50)	2 (28,6)	0,608	2,5
Poor	4 (50)	5 (71,4)		

Table 5. **Correlation Between Quality of Sleep and Migraine Frequency**

Variable	Migraine Frequency, n (%)		*P Value*	OR
	Mild-Moderate	Severe		
Quality of Sleep				
Good	3 (50)	0	0,2	5
Poor	3 (50)	4 (100)		

Through a bivariate analysis of association between quality of sleep and primary headache frequency, which includes frequency of the overall primary headaches, frequency of TTH, and frequency of migraine, it can be concluded that there is no association between quality of sleep and primary headache frequency.

Multivariate analysis was also conducted to analyze the relationship of confounding variables: depression, anxiety, and stress with the dependent variable of primary headache. Multivariate analysis was performed using the Logistic Regression test at SPSS. The variables included in the multivariate analysis with the dependent variable for primary headache were the variables that in the bivariate analysis obtained p-value <0.250. These variables include sleep quality, depression, anxiety, and stress. After analysis of these three variables are obtained, it was found that quality of sleep has an association with primary headaches (95% CI, 11.055 to 2154.857), whereas depression, anxiety, and stress do not have a significant association with quality of sleep. The results of the analysis are shown in Table 6.

Table 6. **Multivariate Analysis**

Variable	*P Value*	*Odd Ratio*	95% Confidence Interval	
			Lower	Upper
Quality of Sleep	<0,001	154,343	11,055	2154,857
Depression	0,056	16,119	0,932	278,712
Anxiety	0,930	0,901	0,089	9,099
Stress	0,447	3,074	0,170	55,648

This multivariate analysis also shows that depression, anxiety, and stress variables as confounding variables do not cause a change in the OR value of quality of sleep (independent variable) by more than 10%, so these three variables are not confounding variables for the association between quality of sleep and primary headache. The final OR value obtained by the quality of sleep variable is 154.343, so it can also be explained that people who experience poor quality of sleep have a chance of having primary headache 154.343 times more likely compared to people who have good sleep quality.

Discussion

This study aims to see the association between quality of sleep and primary headache in Siloam Karawaci Hospital patients. The variable analyzed for its association with primary headache was quality of sleep. Meanwhile, the confounding variables analyzed were depression, anxiety, and stress. In this study, it was found that quality of sleep variables have a significance value (P=<0.001), indicating that there is a significant association between quality of sleep with primary headache.

A significant association between quality of sleep with primary headaches were found in this study. The same thing is also found in a study conducted by Agus A, 2015, that there is a statistically significant correlation between poor quality with primary headaches (P=<0.001).[7] Cesar F, 2017 suggests that there is a two-way relationship between headaches and poor sleep quality. Poor sleep quality can cause headache and headache can cause poor sleep quality.[4]

In a study conducted by Brit AB, 2014, there is a significant relationship between depression and the incidence of recurrent primary headaches (P = <0.001).[8] The statement is in accordance with the results of this study, which found that depression has a significant value to the relationship with primary headache (P = 0.001).

Analysis of the association between quality of sleep and overall primary headache frequency, TTH, and migraine frequency showed no significant association. Whereas in a study conducted by M. Ichsan AS, 2017, it was stated that sleep quality had a significant relationship with headache frequency (P = 0.001), with a strong correlation (r=0.581).[9] The same thing was stated by Helen FB, 2005, increased headache frequency led to a strong association with sleep disturbances.[6]

The difference results in this study with previous studies can occur because the difference in the number of respondents is quite large between this study and the two studies. There are also differences in the target population and sample characteristics in the form of differences in age, occupation, and habits so that the results obtained are different.

Researchers also observed that most patients with headache complaints would come to the hospital for treatment if the complaints they experienced disturbed the patient's activity and sleep quality, moreover, most patients with headaches prefer to rest at home. This is thought to be one of the things that can affect the results obtained by researchers.

After multivariate analysis, significant results were found only on the variable quality of sleep. Meanwhile, depression, anxiety, and stress were also included in the multivariate analysis showing insignificant association results. This eliminates the notion of depression, anxiety, and stress as confounding variables for the association between quality of sleep and primary headache.

This study has several weaknesses such as the research methods used can not assess the causal relationship between sleep quality with other variables. This study also uses subjects in certain populations and places so that the results obtained may not necessarily describe the same conditions in different populations and places. There are several strengths in this study, such as the discovery of a significant association between quality of sleep and primary headache (p <0.001), filling out the research questionnaire conducted by interview so that there is no difference in perceptions in filling and using a validated questionnaire.

Conclusion

There was a significant association between quality of sleep and primary headache among subjects. However, there was no association between quality of sleep and overall primary headache frequency, TTH frequency, and migraine frequency. Patient who experience poor quality of sleep have a chance of having primary headache 154.343 times more likely compared to people who have good sleep quality.

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Clinical Spectrum of Neurological Complaints in COVID-19: Experiences from a COVID-19 Referral Hospital in Indonesia

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Abstract

Background : The main feature of COVID-19 is symptoms of respiratory system disorder, however there has been an increase in reports of neurological symptoms that appear in COVID-19 patients. Several previous studies have linked SARS-CoV-2 with nervous system damage. Research studying neurological complaints in confirmed COVID-19 patients in Indonesia is still lacking

Aim: To identify neurological, laboratory and imaging findings in COVID-19 patients with neurological symptoms.

Methods: This study was a cross-sectional observational study conducted at Siloam Hospitals Mampang, a COVID-19 referral hospital in South Jakarta. We analyzed medical records of confirmed COVID-19 patients during the period of April - July 2020. The data collected included demographic data, comorbidities, neurological manifestations, laboratory examinations, and neuroimaging.

Results: There were 22 confirmed COVID-19 patients with neurological complaints referred to a neurologist. The mean age of patients was 60.4 (SD 15.8) years. The most common neurological complaints were altered mental status (50%), hemiparesis (27.3%), and tremor (22.7%). More than half of the patients (81.8%) had a comorbid condition or past history related to neurological symptoms. Laboratory examination results showed increased NLR (neutrophil-lymphocyte ratio) (50%), anemia (45.5%), and leukocytosis (40.1%). The most common neuroimaging feature was infarct (50%) in Brain CT scan.

Conclusion: The neurological complaints in COVID-19 patients are mostly associated with exacerbation of pre-existing comorbidities as a result of the severe inflammatory process triggered by COVID-19. Further research is needed to establish the mechanism of nervous system dysfunction in COVID-19

Background

Since first reported in Wuhan at the end of 2019, the SARS-CoV-2 virus, which caused the viral pneumonia outbreak known as COVID-19, has spread to more than 215 countries.[1] As of July 2020, there has been approximately 18 million confirmed cases with a fatality of 700 thousand cases.[2] SARS-CoV-2 is an enveloped, non-segmented, single-strand RNA virus with a diameter of 65-125 μm, and preferentially infects cells of the respiratory tract.[3,4] Symptoms of COVID-19 vary between individuals, ranging from mild to life-threatening conditions such as respiratory failure, septic shock, and multiorgan failure.[5] Based on a previous study conducted by Chen et al, the most common symptoms complained among COVID-19 patients include fever, cough, fatigue, dyspnea, sore throat, headache, and conjunctivitis.[6] Severe manifestations were predominantly found in the elderly and patients with pre-existing comorbid conditions, such as hypertension and diabetes.[6,7]

Although the primary manifestations of COVID-19 involve the respiratory system, there has been increasing reports of neurological symptoms in COVID-19 patients.[8] Nervous system involvement may be caused by direct invasion of the central nervous system (CNS) by the virus, immune-mediated inflammation, or as complications due to the systemic effects of COVID-19.[8,9] A systematic review conducted by Nepal et al revealed that the most frequently encountered neurological symptoms include disorders of smell (59%), taste (56%), myalgia (25%), and headaches (20%). Research that studies neurological manifestations in confirmed COVID-19 cases in Indonesia is very lacking. Therefore, we conduct this study in order to identify clinical, laboratory, and imaging findings on COVID-19 patients with neurological complaints.

Methods

Study design and population

This study was a cross-sectional observational study conducted at Siloam Hospitals Mampang, a COVID-19 referral hospital in South Jakarta. The patients included in this study were confirmed COVID-19 patients with complaints of neurological symptoms, and were referred to a neurologist during that period. We analyzed medical records belonging to COVID-19 patients confirmed by real-time reverse transcriptase polymerase-chain-reaction (rt-PCR), collected via nasopharyngeal swab, during the period of April - July 2020.

Data collection

The data obtained were secondary data from medical records. Demographic data collected include age, gender, presence of pre-existing comorbidities, and past medical history. The neurological symptoms described were complaints that necessitated a referral to neurology, or the chief complaint that resulted in patient admission. Examination of vital signs were obtained from the emergency department, or the last examination done at the isolation ward. Neurological evaluation and examination was conducted by a neurologist. Laboratory test results included complete blood count and other significant results. Imaging examinations were performed according to the anatomical sites of the neurological complaint. Neurological diagnosis was made by a neurologist according to clinical, laboratory, and radiological findings.

Results

During April - July 2020, there were 22 confirmed COVID-19 patients with neurological complaints. Of the 22 patients, 13 (59.1%) were female and 9 (40.9%) were male. The mean age of the patients was 60.4 (SD 15.8) years old. Demographic data, clinical, laboratory and imaging findings detailed in Table 1. Characteristics of pre-existing comorbidities, past history, neurological manifestations and diagnoses were presented in Table 2. More than half of the patients

(81.8%) had comorbid conditions or past medical history associated with neurological symptoms. The most complained neurological symptom was altered mental status (50%), followed by hemiparesis (27.3%), and tremors (22.7%). Ischemic stroke was found in 6 cases (27.3%). Laboratory examination results (Table 3) showed an increased NLR ratio (50%), anemia (45.5%), and leukocytosis (40.1%). Out of the 10 patients who underwent brain imaging examination (Table 3), 6 (50%) of them showed an ischemic / infarct

Table 1. Summary of demographic data and clinical features

No	Age (years)	Gender	Comorbidities/ Past History	Neurologic manifestations	Vital signs	Laboratory results	Imaging results	Diagnosis
I	63	Male	DM, HT, history of ischemic stroke 1 month ago	Loss of consciousness and right hemiparesis since 2 days ago	GCS: E4M6V5 BP: 120/70, HR: 105, RR: 20 (on ventilator), T: 37.2	Hb: 9.2, WBC: 12.4, thrombocyte 170, BG 204, K: 3.3, albumin: 3	Infarct	Ischemic stroke + DKA
II	46	Female	History of colorectal carcinoma	Delirium, recurrent general seizure (3 times,duration 5 minutes each, duration of alertness between seizure was 15 minutes) since 1 day ago	GCS: E4M6V5 BP: 104/60, HR: 90, RR: 18, T: 37.1, SpO2:99%	Hb: 11, WBC 23.3, segmented neutrophil:l: 88%, lymphocyte: 6%, NLR: 15, thrombocyte 448, Na: 117, K: 5.6, CRP: 5.3	NR	Metastatic brain tumor
III	98	Female	History of AF	Loss of consciousness, left hemiparesis, and myoclonic	GCS: E1M1V1 brainstem reflexes (-)	NR	Brainstem infract	Ischemic stroke + AF
IV	47	Male		Loss of appetite since 1 weeks ago, left hemiparesis since and left central facial nerve palsy since 1 days agp	GCS:E3M5V4 BP: 144/86, HR: 96, RR: 30, T: 37.8, SpO2: 94%	Hb: 12.8, WBC: 13.7, thrombocyte 658, segmented neutrophil: 86%, lymphocyte: 4%, NLR: 21.5, BG: 226	Infarct	Ischemic stroke
V	57	Male	DM, HT, History of ischemic stroke 6 months ago	Delirium and tremor since 2 days ago	GCS: E4M5V4 BP:120/80, HR:74, RR:20, T:37, SpO2: 99% E4M5V4	Hb: 12, WBC: 21, segmented neutrophil: 93%, lymphocyte: 2%, NLR: 46.5, ureum 85, creatinine: 4.5, Na: 117, K: 1.01	Old infarct	Metabolic encephalopathy +hyponatremia
VI	70	Male	History of Alzheimer's Disease with parkinsonism, bed ridden	Dyspnea since 1 week ago, accompanied by tremor and rigidity	GCS: E4M6V5 BP: 126/88, HR: 87, RR: 24, T: 37.1	Hb: 12.1, WBC: 20, ESR: 45, segmented neutrophil: 87%, lymphocyte: 4%, NLR: 21.75, LDH: 437, Na: 130	NR	Alzheimer's Disease + parkinsonism
VII	76	Female	History of lung carcinoma	Aphasia since few months ago, fever and dyspnea since 1 days ago followed by loss of consciousness	GCS: E4M4 aphasia BP: 110/70, HR: 78, RR: 22, T: 39	WBC: 5.8 , segmented neutrophil: 61%, lymphocyte: 27%, NLR: 46.5	Multiple hyperdense lesions and multiple bleeding on right frontal and left parietal lobes.	Metastatic brain tumor
VIII	64	Female	History pulmonary embolism on heparin	Left hemiparesis and left central facial nerve palsy since 1 day ago	GCS: E4M6V5 BP: 215/120, HR: 88, RR: 18, T: 36	WBC: 12.1, segmented neutrophil: 77%, lymphocyte: 19%, NLR: 4.05, INR: 0.91, BG: 313, HbA1c: 14.1, Na: 135, D-dimer: 0.62	Acute infarct on basal ganglia,right frontoparieta l lobes, subacute infarct on left thalamus	Ischemic stroke
IX	77	Female	History of craniotomy because of intracranial	Loss of consciousness since 1 day ago	GCS: E4M6 aphasia BP: 137/99, HR: 81, RR: 20, T: 37.5	Hb: 9.4, WBC: 9.7, segmented neutrophil: 68%, lymphocyte: 17%, NLR: 4, Na: 133, K: 6.2,	NR	Epilepsy

			aneurysm rupture 7 years ago			AST: 66, ALT: 77, creatinine: 1.48		
X	64	Male	HT, history of ischemic stroke 1 week ago	Recurrent tonic seizure (duration of each seizure: 5 minutes) since 1 day ago	GCS: E4M6V5 BP: 160/100, HR: 60, RR: 20, T 37.1	WBC: 11.38, segmented neutrophil: 71%, lymphocyte: 14%, NLR: 5.07, ureum: 85, creatinine 2	NR	Acute symptomatic seizure
XI	80	Female	History of femur fracture 1 year ago, history of Alzheimer's Disease	Disatria and disfonia since 3 months ago, cough and dyspnea since 1 day ago. Physical exam: left LMN hypoglossal palsy	GCS: E4M6V5 BP: 147/75, HR: 94, RR: 30, T: 37.5	WBC: 6, segmented neutrophil: 63%, lymphocyte: 18%, NLR: 3.5, aPTT: 40.5 (control:30) , PT 12.6 (control: 10.9), INR: 1.17, albumin: 3.37, Na: 135, CRP: 99.14	Head CT-Scan: chronic SDH	Chronic SDH + AD
XII	58	Female	HT, History of ischemic stroke 5 months ago,	Tremor on right extremity, left hemiparesis, and pelvic pain since 6 days ago	GCS: E4M6V5 BP: 122/78, HR: 87, RR: 22, T: 37	TSH HS: 0.41, Free T4: 16.83	Xray: old fracture column femur	Parkinsonism
XIII	45	Female	Obesity, sepsis, DM, post myocarditis, history on mechanical ventilation for 20 days	Tetraparesis since 1 month ago	GCS: E4M6Vett BP:120/94, HR: 88, RR: 20, T: 36	Hb 8.8, WBC: 17.27,segmented neutrophil: 70%, lymphocyte: 13%, NLR: 5.38, CRP: 66.5, PT: 13.4 (10.2), aPTT: 53.4 (control 33), D-dimer: 1.99	NR	Susp MG (respon on mestinon), dd hipokalemia
XIV	38	Male		Recurrent pain in both thighs and radiating to calf since 5 days ago, no history of trauma. Physical findings: tenderness on thigh	GCS: E4M6V5 BP: 120/87, HR: 88, RR: 21, T: 37	Hb 10.6, WBC 3.87, segmented neutrophil: 59%, lymphocyte: 25%, NLR: 2.36, AST: 66, ALT: 74, CRP: 35, Na: 130, K: 3.2	NR	Myalgia
XV	71	Female	HT, NSTEMI, on heparin medication	Loss of consciousness since 1 day ago, gross hematuria and petechiae	GCS: E3M5Vett BP: 171/88, HR: 93, RR: 15, T: 37.1	Hb 9.6, WBC 19.5, segmented neutrophil: 81%, lymphocyte: 6%, NLR: 13.5, PT: 10.4 (control 10.2), INR: 1.13, aPTT :40.1 (control 35.4) AST: 42, ALT: 51, ureum: 123.3, creatinine: 1.36	Infarct in brainstem	Brainstem ischemic stroke
XVI	40	Male	History of Parkinson Disease for 5 years	Dyspnea, cough, fever, and tremor since 2 weeks ago	GCS: E4M6V5 BP: 119/87, HR: 88, RR: 21,T: 37	NR	NR	Parkinsonism
XVII	55	Female	History of right lung chondrosarcoma and hyperthyroid for 1 year,	Paraparesis (unable to walk) and paresthesia since 3 weeks ago	GCS: E4M6V5 BP: 98/72 (on norepinefrin), HR: 105, RR: 24, T: 37	FT4: 65, TSHS <0.05, albumin: 2.72	PET-Scan: increased FDG uptake in right lung superior lobe and multiple lymph nodes	Polyneuropathy + paraneoplastic syndrome
XVIII	26	Female		Tremor of both hands, abdominal pain, fever, and myelena since 1 weeks ago	GCS: E4M6V5, BP: 114/87, HR: 90, RR: 28, T: 38.3	Hb: 7.4, WBC: 4.7, thrombocyte: 66, segmented neutrophil: 79%, lymphocyte: 17%, NLR: 4.68, ureum: 74, creatinine: 1.8, AST: 100, ALT: 91, PT 15.1 (control 13.8), aPTT 33(control: 30), fibrinogen: 123, D-dimer: 11.120,	Head CT-Scan: normal	Myoclonic on CKD

XIX	65	Male	DM, history of low back pain since 2 years ago	Delirium and worsened low back pain since 3 days ago	GCS: E1M5V2 BP: 119/75 (on norepinephrine), HR: 105, RR: 25, T: 36.9	NR	Head CT-Scan: normal	Metabolic encephalopathy + DKA
XX	69	Female	History of colorectal carcinoma, sepsis	Loss of consciousness and right hemiparesis	GCS: E1M3Vett, BP: 105/82, HR: 94, RR: 22, T: 36.8	NR	Head CT-Scan: acute infarct left basal ganglia	Stroke ischemic
XXI	54	Female	HT	Low back pain since 1 week ago with history of falling 2 weeks ago	GCS: E4M6V5, BP: 148/75, HR: 62, RR: 18, T: 37	NR	Xray: compression fracture L1	Compression fracture L1
XXII	66	Male		Loss of consciousness for 30 minutes 1 week ago, general weakness	GCS: E4M6V5, BP: 105/70, HR: 88, RR: 20, T: 36.9	Hb 14.2, WBC: 6, thrombocyte: 156, segmented neutrophil: 67%, lymphocyte: 26%, NLR: 2.57, ESR: 40, CRP: 60, AST: 80, ALT: 75, LDH: 909, Na: 125, K: 2.4	Brain MRI: normal	Metabolic encephalopathy + hypokalemia hyponatremia

NR: not reported, DM: diabetes mellitus, HT: hypertension, AF: atrial fibrillation, DKA: diabetic ketoacidosis, GCS: Glasgow Coma Scale, CT: computed tomography, MRI: magnetic resonance imaging, BP: blood pressure (mmHg), HR: heart rate (x/minutes), RR: respiratory rate (x/minutes), T: temperature (^{0} Celsius), Hb: hemoglobin (g/dL), WBC: white blood cell (x 10-3/mL), thrombocyte (x 10-3/mL), BG: blood glucose (mg/dL), NLR: neutrophil:a lymphocyte ratio, CRP: C-reactive protein (mg/dL), Na: natrium (mmol/L), K: kalium (mmol/L), LDH: lactate dehydrogenase (IU/L), INR: International Normalized Ratio, PT: prothrombin time (seconds), aPTT : activated partial thromboplastin time (seconds), ESR: erythrocyte sedimentation rate (mm/h), TSH: thyroid stimulating hormone (mU/L), FT4: free T4 (ng/dL), AST: aspartate transaminase (U/L), ALT: alkaline transaminase (U/L), ureum (mg/dL), creatinine (mg/dL), D-dimer: mcg/mL, fibrinogen (mg/mL), albumin (g/dL)

Table 2. Characteristic of clinical features

	Total (n)	Percentage(%)
Comorbidities/Past history		
HT	6	27.3
DM	3	13.6
Obesity	1	4.5
Ischemic Stroke	4	18.2
Malignancy	4	18.2
Colorectal	2	9.1
Lung	2	9.1
AF	1	4.5
Alzheimer's Disease	2	9.1
Parkinson Disease	1	4.5
Parkinsonism	1	4.5
Pulmonary emboli	1	4.5
Rupture aneurysm	1	4.5
Fracture femur	1	4.5
Sepsis	2	9.1
Myocarditis	1	4.5
NSTEMI	1	4.5
Neurological manifestation		
Altered mental status	11	50
Loss of consciousness	8	36.4
Delirium	3	13.6
Hemiparesis	6	27.3
Seizure	2	9.1
Tremor	5	22.7
Tetraparesis	1	4.5
Paraparesis	1	4.5
Myoclonia	1	4.5
Dysatria	1	4.5
Dysphonia	1	4.5
Pain	4	18.2
Pelvic pain	1	4.5
Low back pain	2	9.1
Thigh pain	1	4.5
Aphasia	1	4.5
Unilateral facial weakness	2	9.1
Neurological diagnosis		
Ischemic stroke	6	27.3
Metastatic brain tumor	2	9.1

Metabolic encephalopathy	3	13.6
Alzheimer's Disease	3	13.6
Myoclonic on CKD	1	4.5
Epilepsy	1	4.5
Acute symptomatic seizure	1	4.5
MG	1	4.5
Compression fracture	1	4.5
Parkinsonism	3	13.6
Chronic SDH	1	4.5
Myalgia	1	4.5
Polyneuropathy ec paraneoplastic syndrome	1	4.5

Discussion

Altered mental status

The most frequently encountered neurological complaint was altered mental status (50%), followed by hemiparesis (27.3%) and tremors (22.7%). This result is similar to the study conducted by Helms et al, in which altered mental status was found in 69% of confirmed COVID-19 patients admitted to the ICU.[10] The mechanism of altered mental status in COVID-19 is still unclear. SARS-CoV-2 has been shown to have neurotropic features that enable it to invade the CNS directly via attachment to ACE2 receptors in capillaries, or via penetration of the cribriform plate through the olfactory nerve.[11,12] However, direct invasion as the cause of COVID-19 encephalopathy is still doubtful, as several studies report that positive CSF-PCR examinations were only found in less than 10% of cases.[13] An interesting theory is the possibility of severe systemic inflammation caused by cytokine storm as the main mechanism of cerebral damage in COVID-19.[14] Several studies showed that there was a significant increase in pro-inflammatory cytokines in the CSF of COVID-19 patients with encephalopathy [15,16,17], as well as a significant improvement in response to intravenous steroids.[15,18,19] The possibility of autoimmune mechanisms can also be considered, given the relationship between COVID-19 and GBS (Guillain Barre syndrome) [20] and clinical improvement with the administration of immunotherapy (intravenous immunoglobulin 15[,18,19] and plasmapheresis[17]).

Ischemic stroke

Ischemic stroke occurs in 27.3% of patients, with the most common clinical feature of altered mental status and hemiparesis. The results of our study revealed a higher incidence of stroke than in the study conducted by Mao et al, which showed that acute cerebrovascular disease occurred only in 6% of COVID-19 cases.[21] This difference may be due to variations in the study sample, in which our sample was COVID-19 patients who complained of neurological symptoms (n = 22), while the study conducted by Mao et al included all COVID-19 patients in general (n = 214). This made our sample more likely to have more severe conditions, as evidenced by the examination of inflammatory markers that tend to be higher in our study. The

number of subjects with pre-existing comorbidities were higher in our sample compared to the study by Mao et al (81% vs 38%).[21] The underlying cause of ischemic stroke in COVID-19 is thought to be COVID-19-associated-coagulopathy (CAC), which appears in acute systemic inflammatory response, mediated by cytokines and proinflammatory agents. The CAC is characterized by an increase in blood coagulant markers (D-dimers, fibrinogen degradation products, fibrinogen), as well as peripheral inflammation markers (CRP), and mild thrombocytopenia.[22] In severe conditions of COVID-19, coagulopathy can also occur with a pattern similar to disseminated intravascular coagulation (DIC), due to excessive consumption and activation of coagulation factors, characterized by increased PT, aPTT, and D-dimer, and thrombocytopenia. [22.23]

Anemia

Anemia was present in 45.5% of cases, with a mean hemoglobin value of 10.29 (SD: 1.61). SARS-CoV-2 can cause anemia through various mechanisms. The interaction of SARS-CoV-2 with hemoglobin receptor molecules such as ACE2, CD147, and CD26 will induce a reaction between spike protein and

membrane receptors, triggering viral endocytosis.[24] Further hemolysis occurs through damage to the heme on 1-beta-chain of hemoglobin.[25] By activating CD147 and CD26, SARS-CoV-2 can attack erythroblasts in bone marrow, causing progressive anemia.[24] Free circulating heme caused by hemolysis may damage endothelial, resulting in diffuse endocellitis.[24,26] Previous studies also reported several case reports of autoimmune hemolytic anemia associated with COVID-19, so that the possibility of an autoimmune process should also be considered.[27,28] In this study we were unable to further explore the causes and pathomechanisms of anemia due to limited laboratorium facilities.

Increased NLR Ratio

Out of 22 cases, an increased NLR ratio was found in 11 cases (50%). Increased NLR ratio was associated with severe COVID-19 and a poor prognostic factor. The study conducted by Yan et al showed that the NLR ratio tended to be higher in the non survival group (median: 49.06, interquartile range (IQR): 25.71-69.70) compared to the survival group (median: 4.11, interquartile range (IQR): 2.44-8.12, p <0.01). The study also stated that an NLR more than 11.74 had a significant correlation with hospital mortality (odds ratio = 44,351; 95% confidence interval = 4,627-425,088).[30] The mechanism of increased NLR ratio in COVID-19 is still unclear. The increase in neutrophils occurs due to a hyperinflammatory process in COVID-19, evidenced by an increase of classic neutrophil chemoattractant (CXCL1, CXCL2, CXCL3, CXCL5, CXCL20, and interleukin-8) in cells infected with SARS-CoV-2.[31,32] Lymphopenia can occur due to bone marrow suppression, immune - mediated-destruction, as well as sequestration due to activation of the ACE2 receptor by SARS-CoV2.[33,34] The mean NLR ratio in our study was quite high (16.99, SD: 15.23), but we could not compare the outcome in our sample with that previous study due to lack of data and most of the patients were still in treatment.

Electrolyte imbalance

Electrolyte imbalance was present in 7 cases (31.8%), with the most common abnormality being hyponatremia (6 cases, 28.6%), followed by hypokalemia (4 cases, 18.2%), and hyperkalemia (2 cases, 9.1%). A study conducted by Lippi et al showed that sodium and potassium levels were found to be lower significantly in severe COVID-19.[35] The mechanism of hyponatremia in COVID-19 is still unclear. Previous studies linked syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a cause of hyponatremia in COVID-19 pneumoniae.[36] A study by Berni et al showed that levels of interleukin-6, a pro-inflammatory cytokine core in the COVID-19 cytokine storm, was inversely

related with sodium.[37] This suggests that the systemic inflammatory system may also play a role in the development of hyponatremia. Hypokalemia is thought to occur due to activation of the ACE2 receptor, resulting in decreased ACE2 expression, which in turn triggers an upregulation in angiotensin II, leading to increased excretion of potassium by the kidneys. [37,38] Hypokalemia can also be caused by gastrointestinal loss, such as vomiting and diarrhea, which are common in COVID-19.[37,39]

Correlation of pre-existing comorbidities with neurologic complaint on COVID-19

More than half (81.8%) of the study sample in this study had pre-existing

comorbidities or past history associated with the neurological complaint. These results indicate that it is likely that COVID-19 does not cause direct nervous system damage, but induces dysfunction through the exacerbation of pre-existing neurological disorders, presumably via the hyperinflammation mechanisms. SARS-CoV-2 can cause a widespread inflammatory cascade condition through activation of the ACE2 receptor, leading to severe acute systemic inflammation mediated by interleukin (IL)-6, which increases the number and response of proinflammatory cytokines such as IL-17, IL-21, and IL- 22.[40,41] The cytokine storm causes widespread endothelial dysfunction, including damage to the blood-brain-barrier.[14] SARS-CoV-2 infection, accompanied by comorbidities, tended to be more severe than without comorbidities ($p < 0.03$)[21]. A study conducted by Sarfo et al showed an increase in the recurrent stroke rate during January 2020 - June 2020 compared to the previous year (19.0% vs 10.9%, $p = 0.0026$).[42] Neuroimaging studies conducted by Lu et al showed the possibility of microstructural and functional damage in global gray matter volume (GMV), GMVs in the left Rolandic operculum, right cingulate, bilateral hippocampi, left Heschl's gyrus. Global MD of WM in COVID-19 were correlated with memory loss [43], so there may be decline in cognitive function, especially in patients with pre-existing dementia.

Limitation

The limitation of our study is that we cannot perform more specific laboratory tests, so we could not further investigate the causes of abnormal laboratory results. Furthermore, neuroimaging and some laboratory tests were not performed in all patients, so we could not compare and describe the data.

Conclusion

We have found that neurological complaints in COVID-19 patients are mostly associated with exacerbation of pre-existing comorbidities as a result of the severe inflammatory process triggered by COVID-19. Further research is needed to establish the mechanism of nervous system dysfunction in COVID-19.

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Use Of Panty Liner As A Risk Factor The Occurration Of Abnormal Vaginal Discharge

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Abstract

Vaginal discharge or fluor albus is a problem that is often found in women. Daily use of panty liner is a predisposing factor of pathological/ abnormal vaginal discharge. This paper reviews the correlation between the use of panty liner and vaginal discharge. The aims of this study were to analyze the effect of daily panty liner use as a risk factor of vaginal discharge. This research is done by using cross-sectional method. Study population is students of University of Pelita Harapan in Faculty of Nursery. Sample size calculation was done using the categorical comparative analytical formula and a result 46 samples were obtained for each population. Questionnaire was used in this research. Statistical analysis is done by using the SPSS 22.0 program with Chi Square method. Bivariate analysis on 92 respondents revealed that there is a significant association between the usage of panty liner and abnormal vaginal discharge (p value <0.05). Based on bivariate analysis panty liner material is not related to abnormal vaginal discharge (p value >0.05).

Introduction

One of the factors that affect health problems in the female reproductive organs is abnormal vaginal discharge. Discharge that comes from a woman's genitalia outside the menstrual period and is not in the form of blood is called vaginal discharge or fluor albus.[1] Vaginal discharge can be both physiological and pathological. Vaginal discharge is said to be physiological if it is odorless, colorless/ whitish, and does not feel itchy. A vaginal discharge is said to be pathological if the discharge becomes yellowish, itchy, and foul-smelling.[2] Women of all ages can experience vaginal discharge-.Women aged 15-24 years experienced vaginal discharge as much as 3l.8% according to a survey conducted by the Indonesian Adolescent Reproductive Health Survey (SKRRI). Based on the results of research on women's reproductive health, 75% of women in the world have experienced vaginal discharge and 45% of them experience recurrent vaginal discharge.[2] The prevalence of vaginal discharge often increased, in 2002, 50% of women experienced vaginal discharge. In 2003 this figure increased to 60% and to 70% in 2004.[3] This increase in percentage was due to the tropical climate in Indonesia. This condition causes the feminine area to become moist so that the fungus can easily develop and cause vaginal discharge.[4]

Abnormal vaginal discharge can be caused by infection or non-infection. Non-infectious causes that can cause vaginal discharge

include abnormalities of the reproductive organs that can be caused by tumors or malignancy. There are also factors that trigger vaginal discharge, such as diabetes, urinary tract infections, use of contraceptive pills and use of panty liners.[5, 6]
Indonesian women still think that the use of panty liners can protect their feminine area.[7] In fact, the use of panty liners can make the use of panty liners moist and can cause vaginal discharge. Based on research by Farage (2007), 10-30% of women in North America and Western Europe always use panty liners outside of their menstrual period, this is based on their desire to keep their female area clean and dry.[8] However, there is no data that states the percentage of panty liner users in Indonesia. The panty liner does not have a significant difference with ordinary pads, what distinguishes the two is the size of the panty liner which is thinner than ordinary pads.[9] In addition, according to research by Farage (2007), the use of panty liners can reduce the number of Lactobacillus species which are normal flora in the vagina, and can increase the number of bad bacteria in the vagina, namely Eubacterium species. The use of panty liners can also cause intestinal flora such as Eschericia coli to enter the vagina.[9] Research that has been conducted at the Faculty of Medicine, University of Andalas Padang (UNAND) and Aisyiyah University Yogyakarta, the use of panty liners can trigger vaginal discharge. It is stated that there is a relationship between the use of panty liners and the incidence of vaginal discharge (69.2%).[10] The results of research conducted by Aisyiyah University Health Sciences Yogyakarta also showed 56% of women who use panty liners experience vaginal discharge.[6] According to the International Journal of Gynecology & Obstetrics, from four studies on the use of panty liners, there was no effect on the appearance of vaginal discharge, only one study supported the influence between the use of panty liners and vaginal discharge.[11] Another journal research conducted by the International Journal of Gynecology & Obstetrics, also stated that 95% of women who use panty liners do not experience problems with vaginal discharge.[12] There are still pro and contra regarding this problem, so further research is needed to prove the effect between the two.

Research Design and Sample

This research was conducted with a quantitative analytic research type with cross sectional method with case control. The sample size estimation of this study was calculated using unpaired categorical comparative analytic method. The total sample required in this study was 92 people.
In this study, samples that use panty liners and those who do not use panty liners are needed. The inclusion criteria in this study included female students of the Faculty of Nursing, Pelita Harapan University, 18-25 years. Subjects with Diabetes Mellitus and organic reproductive organ disorders (uterine tumors) were excluded.

Data and Statistical Analysis

Data obtained using primary data, where data is taken directly through questionnaires The data obtained from the study will be tabulated and analyzed.data tabulation will be performed using Microsoft Excel 2010

program and data analysis will be performed using SPSS 22.0 program. Statistical tests are conducted to prove the hypothesis. The method used for normal distribution is Chi2. The method for abnormal distribution will be analyzed using Fisher's Test

Results and Discussion

Characteristics of Research Subjects:

Table 1. Age Distribution in the Panty Liner User Group

Age	(n=46)	Percentage (%)
18 years	3	6
19 years	11	24
20 years	22	48
21 years	10	22
22 years	0	0

The age distribution in the majority of panty liner users is 20 years old, as many as 22 people. Then followed by the age of 19 years, totaling 11 people. A total of ten respondents were 2l years old and there were three respondents who were 18 years old. There were no respondents aged 22 years who used panty liners (Table 1).

Table 2. Age Distribution in the Non-Panty Liner User Group

Age	(n=46)	Percentage (%)
18 Years	2	4
19 Years	18	40
20 Years	16	35
21 Years	8	17
22 Years	2	4

For the age distribution in the non-wearing panty liner group, it was found that the majority of respondents were 19 years old as many as 18 respondents. 16 respondents aged 20 years and eight respondents aged 2l years. There are two respondents aged 18 years and also two respondents aged 22 years (Table 2).

Table 3. Results of Bivariate Analysis of Pantv Liner and Abnormal Vaginal Discharge

Variabel	No Abnormal Vaginal Discharge	%	Abnormal Vaginal Discharge (n)	%	Total (n)	%	OR (95%CI)	P value
Non-panty liner	35	76.1%	11	23.9%	46	100%	5.428 (2.198-13.450)	0.001
Panty liner	17	37%	29	63%	46	100%		
Total	52	56.5%	40	43.5%	92	100%		

Data from research results that have been statistically tested with Chi Square, obtained a P value of 0.001 where the P value is less than 0.05. This has a positive meaning, so it can be concluded that the use of panty liners can be a risk factor for abnormal vaginal discharge (Table 3).

Table 4. Comparison of The Incidence of Abnormal Vaginal Discharge for The Non-users & Users of Panty Liner

	n	Abnormal Vaginal Discharge	%
Non-Panty Liner	46	11	24%
Panty Liner	46	29	76%

Based on table 4, regarding the comparison of the incidence rate of vaginal discharge in panty liner users and those who do not use panty liner, it is found that the number of abnormal vaginal discharge in panty liner users are 29 respondents and 11 respondents in non-panty liner users. Respondents without abnormal discharge in non-panty liners more than those with panty liners as many as 35 respondents. A total of 17 respondents did not have abnormal vaginal discharge even when using panty liners.

Table 5. Data Distribution in Antiseptic & Non Antiseptic Panty Liner User

	Jenis Panty Liner				Total
	Antiseptic		Non-Antiseptic		
	n	%	n	%	
Panty liner	2	4.2%	44	95.8%	46

Two respondents used panty liners containing antiseptic and 44 respondents used panty liners without antiseptics (Table 5).

Table 6. Bivariate Analysis of Panty Liner Types and Abnormal Vaginal Discharge

		Abnormal Vaginal Discharge					*P value*
		Yes (n)	Percentage (%)	No (n)	Percentage (%)	Total	
Types of Panty Liner	Antiseptic	1	3%	1	6%	2	
	Non-antiseptic	28	97%	16	94%	44	
Total		29	100%	17	100%	46	0.614

From the results of the bivariate analysis in table 6, 28 respondents experienced abnormal vaginal discharge when using non-antiseptic panty liners and 16 respondents did not experience abnormal vaginal discharge when wearing non-antiseptic panty liners. There is one respondent who has vaginal discharge when wearing an antiseptic panty liner but another respondent does not have vaginal discharge when using an antiseptic panty liner. The p-value for non-antiseptic-based panty liners was 0.608. The p value for panty liner containing antiseptic is 0.709. The total p-value is 0.614. It can be concluded that the type of panty liner is not a risk factor that affects vaginal discharge

because the p value is not significant (p value> 0.05).

In this study, there is a relationship between the used of panty liners on the risk of abnormal vaginal discharge. Using panty liners increased the risk of abnormal vaginal discharge five times compared to those who did not use panty liners. Types of panty liners that contain antiseptic or not contain antiseptic; does not have a significant relationship with vaginal discharge. The use of panty liners has a significant effect on the risk of vaginal discharge with a bivariate analysis value (p value 0.001; OR 5.428). Too often use panty liners can trigger vaginal discharge because it can make the feminine area becomes moist. Based on research conducted by Runeman et al in 2003, the use of panty liners raises the temperature of 1.50C in the vulvar area and can also increase the pH by 0.6.4 The moist feminine area is also a predisposing factor for candidiasis.[3] Other than that, panty liner that is containing chlorine can kill the normal flora in the vagina (Lactobacillus). Reduced levels of Lactobacillus in the vagina can make the vaginal acidity unstable and become alkaline. An alkaline vaginal pH will make it easier for bad bacteria to grow and thrive.[23]

This research is supported by previous research conducted in the Faculty of Medicine, Andalas University, Padang. Previous research stated that there was a significant relationship between the used of panty liners on abnormal vaginal discharge. The difference between previous studies and this research is that this study examines whether there is an effect of the basic ingredients of the panty liner on the abnormal discharge itself. The results show that there is no significant relationship between the basic ingredients of panty liners on vaginal discharge.

The type of panty liner is not a risk factor for vaginal discharge. Neither panty liner containing antiseptic nor antiseptic did not have a significant effect because the p value > 0.05. This may be because only two people used the type of panty liner that contained antiseptic. Because only two people used the type of panty liner that contained antiseptic, it couldn't cover the entire population, so it's not proven that the type of panty liner that contains antiseptic can prevent vaginal discharge.

In this study it can be said that the bias is quite large. This is due to many confounding factors, including cleanliness vulva, stress, Sexually Transmitted Diseases, wearing tights, and antiseptic. Vulvar hygiene itself includes the direction of cleaning the area femininity, drying of the feminine area, the number of pads used at the time menstruation, underwear material, and number of underwear changes.

Conclusion

In this study, it is known that the use of panty liners can increase the risk of vaginal discharge. It can be seen that the incidence of vaginal discharge in female students who use panty liners is 76% o. The rate of vaginal discharge in female students who did not wear panty liners but vaginal discharge was 24%. Using panty liners can cause vaginal discharge five times greater than not using panty liners. However, the type of panty liner did not have a significant relationship with the occurrence of vaginal discharge.

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Functional Endoscopic Orbital Decompression Surgery in Acute Rhinosinusitis with Orbital Complication : A Case Report

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Abstract

Introduction : Orbital complication secondary to acute rhinosinusitis can cause permanent vision loss and death if not treated promptly and appropriately. The prevalence of orbital complications due to rhinosinusitis is more common in children than adults, occurring in 3-4% of children with acute rhinosinusitis. Lamina papyracea in children has many dehiscences, the nasal cavity tends to be narrowerand the mucosa is softer than in adults, therefore causing the spread of infection more easily from the sinuses to the eyes. Clinical presentation : a 4 year old child presented with eye swelling and pus discharge in the right eye since 5 days before admitted to the hospital, for which she was treated with medication and did not improve. On physical examination, there is a narrow nasal cavity, inferior turbinate edema and hyperemia, mucopurulent discharge. CT scan and MRI revealed contrast enhancement in intraorbitalwith suspected intraorbital abscess with orbital cellulitis, right pansinusitis and buccal abscess. Functional endoscopic orbital decompression was done immediately.
Conclusion : Orbital complication due to acute rhinosinusitis are uncommon but potentially lead to more fatal complications. Early diagnosis and aggressive treatment of immediate functional endoscopic sinus surgery and antiomicrobial therapy have good outcome.

Background

Orbital complication secondary to acute rhinosinusitis can cause permanent vision loss and death if not treated promptly and appropriately. Symptoms that indicate possible intraorbital complications are difficult to open the eyes due to edema, ophthalmoplegia, proptosis, decreased vision, and chemosis. More than 90% cases of orbital abscesses occur secondary to acute or chronic rhinosinusitis, with maxillary and ethmoid sinuses being the most common sources of infection. Other causes include ocular trauma, dacryocystitis, foreign bodies, dental infections (odontogenic), orbital tumors or intraocular tumors, andendophthalmitis.[1]

The prevalence of orbital complications due to rhinosinusitis is more common in children, which occurs in 3-4% of children with acute rhinosinusitis.[2,3,4]

Anatomy of the eye is closely related to the sinuses, especially the maxillary, ethmoid and frontal sinuses. The optic canal is also adjacent to the ethmoid and posterior sphenoid sinuses, lamina papyracea in children is a thin bony plate located between the eye and the ethmoid sinus, which has many dehiscences.[5] The nasal cavity in children tends to be narrower and have softer mucosa, which makes the sinuses easily blocked by mucosal edema during acute infection, and causes the infection to spread from the sinuses to the eye. [2,5]

Case

A 4 year old child presented with eye swelling and pus discharge in the right eye since 5 days before admitted to the hospital. Two weeks

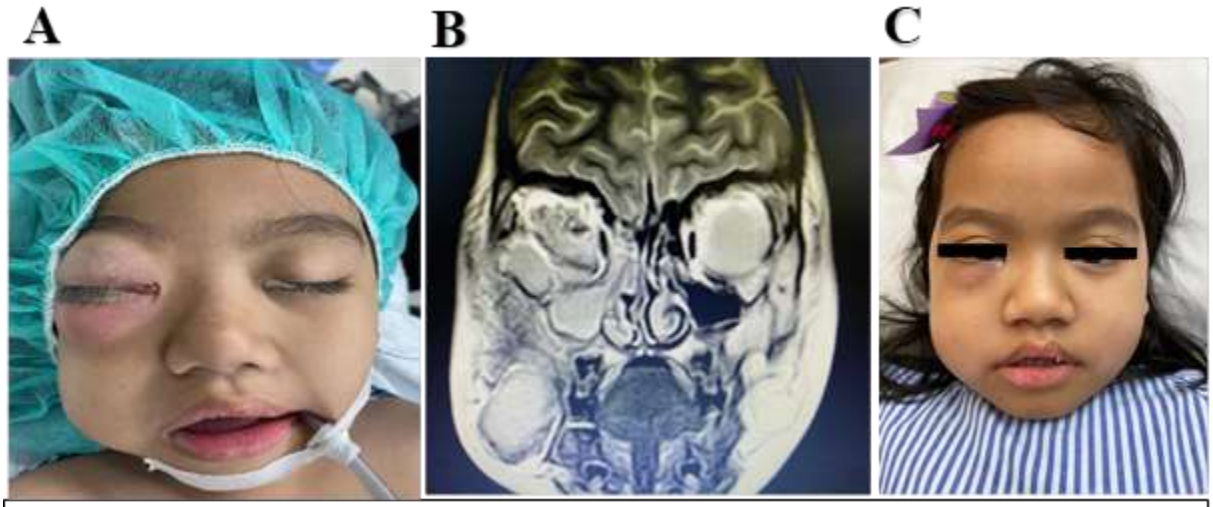

Figure 1. (A) A 4 year old patient with right orbital abscess extending to the lower lid and causing proptosis. (B) Computed tomography (CT) findings demonstrating contrast enhancement in intraorbital suspecting intraorbital abscess with orbital cellulitis, right pansinusitis and buccal abscess. (C) The same patient 7 days after endoscopic sinus surgery and antimicrobial therapy.

Nasoendoscopy was not performed because the patient was not cooperative. Eye examination shows edema in the superior and inferior palpebra, conjunctival chemosis, hyperemia, restricted movement, proptosis and decreased vision in the right eye (1 / ~). CT scan revealed contrast enhancement in intraorbital with suspected intraorbital abscess with orbital cellulitis, right pansinusitis and buccal abscess. An MRI was also performed and revealed to support an intraorbital abscess formation. Patient was given ceftriaxone, metronidazole, ketorolac, and immediate functional endoscopic sinus surgery was done.

Intraoperatively found the middle meatus covered with mucopurulent secret, unsinectomy and middle meatus antrostomy was performed and shows the maxillary sinus was filled with pus and then cleaned, etmoidectomy anterior and posterior was perfomed until lamina papyracea is completely exposed. Lamina papyracea was then removed, the periorbita was opened to reveal orbital fat. The intra orbital abscess bag was opened and the pus was obtained approximately 5cc. An aspiration of the buccal abscess was done and there was 5cc of pus.

First day of postoperative the orbital edema was reduced, and the vision was improved 6/60. Third day of postoperative a nasal toilet was performed under general anesthesia, an open meatus medius was obtained, purulent secretions (+), an open maxillary sinuses with minimal mucoid secretions. Sixth day of postoperative there is a minimal palpebral edema, and vision was restored to normal. The nasal toilet was done under anesthesia shows an open meatus medius with no secretion, the orbital fat was intact, and an open maxillary sinuses. Patient was discharged on the seventh postoperative day with oral therapy and nasal irrigation using NaCl 0,9% 30 cc thrice a day. Follow up on the fourteenth day after surgery found no orbital edema, open middle meatus with no secretions, and normal vision 6/6

Discussion

Rhinosinusitis is defined as inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/ obstruction/ congestion or nasal blockage/ obstruction/ congestion or nasal discharge (anterior/ posterior) +/- facial pain +/- reduction or loss of smell, and either endoscopic signs of nasal polyps and/or mucopurulent discharge from and/or mucopurulent discharge from middle meatus and/or oedema/ mucosal obstruction primarily in middle meatus, and/or mucosal changes within ostiomeatal and/or mucosal changes within ostiomeatal complex and/or sinuses revealed in CT scan EPOS 2020).

Orbital complications associated with acute rhinosinusitis are common in children, accounting for 80% of all complications, and can cause permanent appropriately. The severity of orbital according to Chandler's[4] classification :

1. Periorbital cellulitis : inflammation of the eyelids characterized by edema of the eyelids.
2. Orbital cellulitis : inflammation and edema have extended to the orbit, characterized by proptosis, chemosis and impaired eye movement. Usually can extend to orbital abscess and blindness.
3. Periorbital abscess (subperiosteal abscess): A formation and collection of pus between the periorbita and the orbital bony wall, which characterized by proptosis with changes in the position of the eyeball, impaired eye movement and decreased vision.
4. Orbital abscess : A formation and collection of pus in the orbit characterized by ophthalmoplegia, proptosis and loss of vision
5. Cavernous sinus thrombosis : there has been an extension of infection to the cavernous sinus which characterized by proptosis, ophthalmoplegia, loss of vision accompanied by expansion of signs of infection to healthy eyes and signs of meningitis.

Emergency surgical intervention are indicated in cases of children with large superiosteal abscess or orbital abscess, severe proptosis, ophthalmoplegi, decreased vision and presence of afferent papillary defect.[2,5,6] .

Indications for immediate surgery in this case are decreased vision, proptosis and ophthamolplegia, and the presence of a suspected intraorbital abscess which demonstrated by CT scan. This is also consistent with Sara et al[2] who stated that orbital abscess and subperiosteal abscess are considered emergency cases and are usually treated with immediate surgical drainage to prevent permanent blindness, possible intracranial complications and death. The purpose of the surgery are to drain the abscess, restore intraorbital pressure and restore the sinonasal complex drainage, also to obtain samples for culture. The surgical steps include uncinectomy, antrostomy, etmoidectomy, and penetration of the lamina papyracea. This procedure has several advantages over open procedures, namely eliminating external wounds, reducing postoperative edema, and faster recovery. The success of the transnasal endoscopic approach depends on the expertise of the ENT doctor, amount of local bleeding and the paranasal sinuses involved. According to Yuzhu et al[7], who performed transnasal endoscopic approach in patients with orbital abscesses, they experienced a total improvement approximately 4 to 8 days after surgery.

Conservative treatment can generally be given to patients with Chandler categories 1 to 3. In subperiosteal abscesses with minimal orbital symptoms and abscess size less than 10 mm, conservative therapy is administered and monitored over 24 to 48 hours. If worsening or no improvement within 48 hours, a CT scan needs to be repeated and surgery is

performed immediately. Where as in cases of preseptal cellulitis, the initial treatment is parenteral antibiotic therapy. Conservative treatment with close clinical monitoring may also be considered in cases of orbital cellulitis without visual disturbances or elevated intraocular pressure, with surgical options if worsening or no improvement after 48 hours.

Antimicrobial therapy must cover the causative organism and have sufficient penetration capability into the central nervous system to reduce the risk of intracranial complications.[8] The patient given ceftriaxone in combination with metronidazole intravenously, consistent with most recommendations suggesting a multi-drug combination or a single broad-spectrum antibiotic, to cover polymicrobial pathogens including anaerobes.[8,9] Empirical therapy that can be given is a combination of clindamycin and third generation cephalosporins, vancomycin with or without meropenem, ampicillin-sulbactam, and third generation cephalosporins with metronidazole.[2,9] The patient also given adjunction corticosteroid therapy, this is in accordance with the guidelines for the management of the Infectious Diseases Society of America (IDSA) which recommends giving corticosteroids as an adjunct therapy, especially in patients with a history of allergic rhinitis, and does not recommend giving oral or topical decongestants.[10]

Oral antimicrobial therapy is given according to the results of culture, while patients who did not undergo surgery were given amoxicillin with clavulanic acid or clindamycin for 2 weeks.[10,11]

Conclusion

Orbital complication due to acute rhinosinusitis are uncommon but potentially lead to more fatal complications, therefore requires an aggressive approach. Any case with suspected orbital infection should be treated with antimicrobial therapy and close monitoring. High doses of broad spectrum antimicrobial therapy and steroids should be given immediately in cases of orbital complications with pre-septal cellulitis or periosteal abscess, however, orbital abscess is generally requires surgical approach. Endoscopic sinus surgery gives excellent results if done with good technique and appropriate postoperative care.

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