JURNAL KEDOKTERAN DIPONEGORO
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
JKD, Volume 11, Nomor 2, Maret 2022

CORRELATION BETWEEN FREQUENCY OF TENSION TYPE HEADACHE (TTH) WITH COGNITIVE FUNCTION IN PEOPLE WITH EPILEPSY

Diah Patlika[1*], Herlina Suryawati[1], M. I. Widiastuti[1], Endang Kustiowati[1], Hexanto Muhartomo[1], Arinta Puspita Wati[1]
[1] Department of Neurologi, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
*Corresponding Author : E-mail : diahpatlika.dr@gmail.com

ABSTRACT

Background : Epilepsy is a chronic disease that increases the risk of interictal headaches, one of which is tension type headache. Tension type headache in epilepsy is triggered by recurrent neurogenic inflammation and central sensitization leading to pericranial tenderness affecting on the cognitive function. The frequency of tension type headache in epilepsy is thought to be related to the cognitive function. **Objective :** To determine the correlation between the category of TTH frequency, onset of epilepsy, seizure frequency, age and education with MoCA-Ina score. **Methods :** An analytic observational study with a cross sectional design among forty one epilepsy patients who suffering tension type headache at Dr. Kariadi Hospital, Semarang who met the inclusion and exclusion criteria from April to September 2021. The patients's data was obtained by filling out a questionnaire form. The assessment of the category of tension type headache frequency used ICHD-3 beta 2013 criteria. Assessment of cognitive function used the MoCA-Ina score. Data was analyze with Spearman correlation test then will be tested for partial correlation by controlling the onset of epilepsy and seizure frequency with the significance level p=0.05. **Results :** Forty one epilepsy patients consist of 14 infrequent episodic TTH, 14 frequent episodic TTH and 13 chronic TTH. There was significant correlation between the MoCA-Ina score and the TTH frequency category (rho=0.362; p=0.02), and education level (rho=0.493; p=0.001). **Conclusion :** There was a significant correlation between the TTH frequency in epilepsy with cognitive function.
Keywords : *epilepsy, tension type headache (TTH), Montreal Cognitive Assesment - Indonesian version (MoCA-Ina)*

BACKGROUND

Headache in epilepsy occurs in about 8-15% of the epilepsy population and is related to the duration, intensity of seizures, and the type of epilepsy, furthermore, the prevalence of headache is higher in the polytherapy and drug-resistant epilepsy group.[1] Headache in epilepsy often go undiagnosed because both clinicians and patients focus more on their epilepsy than on the headache itself.[2,3,4,5] The results of a study by Maineri et. al., on 388 adult epilepsy patients showed that the incidence of inter-ictal headache was 48.5%, consisting of migraine (26.3 %), tension type headache (TTH) of 19.1% and other primary headaches (3.1 %).[1,5,6] Nahid et. al., in their study showed that the prevalence of headaches, especially TTH, was significantly higher higher in patients with generalized epilepsy (59%) compared to patients with focal epilepsy (41%).[6]

TTH in epilepsy is produced by a neurogenic inflammatory process due to the vulnerability of brain tissue in patients with epilepsy that triggers headaches through vasoconstriction of smooth muscle blood vessels on the surface of the brain during the process of cortical spreading depression (CSD) resulting in hypoperfusion. Cerebral ischemia results in neurogenic inflammation by producing reactive oxygen species and inflammatory mediators that cause sensitization of perivascular nociceptors in the meninges or brain surface.[7] If this process occurs continuously it causes central sensitization, chronic pain and spasm of the pericranial muscles which is perceived as TTH.[1,6,8] High frequency of TTH represents a high risk of various neuro-inflammatory processes such as cellular edema, gliosis, excitotoxicity-mediated necrosis and neuronal injury in the brain. Neuronal cells that are damaged by this process affect cognitive performance. [6,8,9]

Cognitive disorders are the most common comorbidities in epilepsy, ranging from 20-50% of the epilepsy population. Cognitive impairment occurs in one or more domains such as memory, attention and executive function, with memory impairment being the most common disorder.[10] A study by Witt et al on cognitive function in early-onset epilepsy in adults showed that the high prevalence of cognitive impairment in epilepsy was influenced by seizure frequency.[11]

There is a strong relationship between seizure intensity and the prevalence of TTH in epilepsy.[1,6] The frequency of TTH in epilepsy is thought to be

related to cognitive function scores. The relationship between cognitive and epilepsy has been widely studied, but research on the correlation between TTH in epilepsy and cognitive function has not been conducted.

METHODS

This study is a cross-sectional study, which was conducted at the outpatient neurology department of Dr Kariadi Hospital in Semarang from April to September 2021. The subjects were generalized tonic-clonic epilepsy patients with interictal TTH who received combination therapy of valproic acid and phenytoin for at least 1 year. Meanwhile, the exclusion criteria were epilepsy patients with depression/anxiety, patients with a history of malignancy/brain tumors, and patients who could not read or count.

This research has received permission from the Ethics Committee of the Faculty of Medicine UNDIP with the number 796/EC/KEPK-RSDK/2021 dated April 13, 2021. Patients were selected based on inclusion and exclusion criteria, then informed consent was given to the patient. The study began with a history and physical examination. Then filling out the questionnaire form and examining cognitive function with the MoCA-Ina instrument.

The data were processed using Statistics for Windows 26th version SPSS program to determine the correlation between the frequency of TTH in epilepsy and cognitive function, a correlation test was performed with a 95% confidence level. The confounding variables that consist of the onset of epilepsy, seizures frequency, age and education, will be subjected to a bivariate test using the Spearman correlation test. Then will be tested for partial correlation by controlling the onset of epilepsy and seizure frequency with the significance level p = 0.05.

RESULTS

Table 1. Demographic and Clinical Data

Variable	Frequency Category of Interictal TTH					
	Infrequent TTH (N)	%	Frequent TTH (N)	%	Chronic TTH(N)	%
Demographics						
Gender						
Man	10	24.4	7	17.1	8	19.5
Woman	4	9.7	7	17.1	5	12.2
Age						
Young adults (18-44 years)	14	34.1	12	29.3	12	29.3
Middle (45-59 years)	0	0	2	4.9	1	2.4
Education						
High (Senior High School, Dip, Bac)	13	31.8	11	26.8	11	26.8
Low (elementary, Junior High School)	1	2.4	3	7.3	2	4.9
Clinical						
Onset of epilepsy						
< 5 years	4	9.7	3	7.3	3	7.3
5 – 10 years	3	7.3	3	7.3	0	0.00
> 10 years	7	17.1	8	19.6	10	24.4
Seizure Frequency						
< 12 times/year	2	4.9	4	9.7	5	12.2
12 - 48 times/year	12	29.3	7	17.1	5	12.2
> 48 times/year	0	0	3	7.3	3	7.3
Cognitive (MoCA-INA score)						
Normal (≥ 26)	12	29.3	2	4.9	6	14.5
Abnormal (< 26)	2	4.9	12	29.3	7	17.1

In table 1, the number of subjects in our study was higher in male (60.9%), young adult age group (92.7%) and high education level (85.4%). Meanwhile, according to clinical characteristics, the number of TTH was higher in the group with onset of epilepsy >10 years (61%), the group with seizure frequency 12-48 times/year (58.5%), and the number of subjects with normal cognitive function (48.8%)

was relatively the same as abnormal (51.2%), but if assessed from the category of TTH frequency, the cognitive function score on infrequent TTH tend to be normal, while on frequent and chronic TTH they tend to be abnormal.

Table 2. Correlation of TTH frequency, onset of epilepsy, seizure frequency, age and education with cognitive score

Variable	rho	p
Frequency category of TTH	- 0.362	0.020*
Onset of epilepsy	- 0.225	0.158
Seizure frequency	- 0.251	0.114
Age	- 0.182	0.254
Education	0.493	0.001*

**Spearman Corellation*, p < 0.05, rho = ≥ 0.70 (very strong), 0.40-0.69 (strong), 0.30-0.39 (moderate), 0.20-0.29 (weak), dan 0.01-0.19 (no / negligible) [12]

Table 2 shows a significant correlation with a moderate negative value between the TTH frequency category and cognitive function score in epilepsy patients (rho= -0.362, p=0.02), where the higher the TTH frequency, the lower the MoCA-Ina score. A significant correlation was found with a strong positive value between education and cognitive score (rho=0.493, p=0.001), where the higher the level of education, the higher the MoCA-Ina score. And there was a weak negative correlation between onset of epilepsy and cognitive score (rho= -0.225, p= 0.158), and between seizure frequency and cognitive score (rho= -0.251, p= 0.114). Meanwhile, there was no significant correlation between age and cognitive score (rho= -0.182, p= 0.254).

Table 3. Correlation between onset of epilepsy and seizure frequency in epilepsy accompanied by TTH with cognitive score after controlling for age

Variable	rho	p
Onset of epilepsy		
Before controlled	- 0.225	0.158
After controlled	- 0.109	0.503
Seizure frequency		
Before controlled	- 0.251	0.114
After controlled	- 0.271	0.091

**Spearman Corellation*, p < 0.05, rho = ≥ 0.70 (very strong), 0.40-0.69 (strong), 0.30-0.39 (moderate), 0.20-0.29 (weak), dan 0.01-0.19 (no / negligible) [12]

In table 3, after controlling for age, the correlation between onset of epilepsy and cognitive score was getting weaker (rho= -0.109), while the correlation between seizure frequency and cognitive score was getting stronger (rho= -0.271) with a weak negative value.

DISCUSSION

Based on the demographic characteristics in table 1, the number of subjects in our study was higher in male and young adult group (18-44 years). Possibly this was caused by productive age and the dominant role of men in work so they tend to be more alert to various clinical conditions such as headaches, epilepsy and cognitive disorders that can interfere with their productivity at work, so in our study the group tends to be earlier to come for treatment. The significant number of young adult subjects in our study is in accordance with the literature which states that the onset of TTH in general population is between the second or third decade of life, mostly between 25 and 30 years old, but the peak prevalence increases at the age of 30-39 years old.[13] Whereas in epilepsy, a study conducted by Maineri et al in Italy (2015) on 388 adult epilepsy patients, showed the occurrence of inter-ictal

headache of 48.5% (188 people), of which TTH was 19.1% (74 people) with the range of age was about 40.34 ± 16.46 years old.[1] The number of subjects in high education level groups was higher in our study because their awareness and knowledge about health and the ability to reach the health access tend to be better.

Based on the clinical characteristics in table 1, it was found that the number of subjects with TTH was higher in the group with onset of epilepsy >10 years. In old or chronic epilepsy, it is generally difficult to be seizures free, thus requiring regular control of the patient, the level of adherence to come to the hospital in this group tends to be high. In addition, according to the results of Maineri et al study which showed that inter-ictal TTH occurred at the mean duration of epilepsy is about 19 years (range from 10-28 years).[1] The group of subjects with onset of epilepsy >10 years in our study tended to develop into chronic TTH. Prolonged and recurrent epilepsy increases the risk of CSD-induced neurogenic inflammation leading to central sensitization of nociceptive pathways in the central nervous system due to prolonged nociceptive stimuli in pericranial muscle tissue. This is responsible for the conversion of episodic TTH to chronic TTH.[5]

In general, TTH was also more common in the group of subjects with higher seizure frequency (12-48 times/year) than in the group with lower seizure frequency (< 12 times/year). This is in accordance with the literature which states that headache in epilepsy is related to the duration, severity or intensity of seizures, and the type of epilepsy. The prevalence of headache is higher in the drug-resistant epilepsy, polytherapy and higher seizure frequency.[1.6] The number of subjects with normal cognitive function (48.8%) was relatively same as abnormal (51.2%) in our study, but if assessed from the category of TTH frequency, cognitive function in infrequent TTH tend to be normal (MoCA-Ina 26), whereas in frequent and chronic TTH tend to be abnormal (MoCA-Ina < 26).

Based on table 2 in this study, there was a significant correlation with a moderate negative value between the TTH frequency category and cognitive function scores in epilepsy patients (rho= -0.362, p=0.02), where the higher the TTH frequency, the lower the MoCA-Ina score. Epilepsy is a chronic process that causes epilepsy patients to have a greater chance of suffering from headaches, one of which is TTH.[1] TTH itself is produced by a neurogenic inflammatory process due to the vulnerability of brain tissue in epilepsy which triggers headaches by constriction of the smooth muscles of blood vessels in the brain surface during the process of CSD resulting in hypoperfusion and ischemia. Cerebral ischemia results in neurogenic inflammation and neuronal injury, generating reactive oxygen species and inflammatory mediators (CGRP; calcitonin gene-related peptide, cAMP: cyclic adenosine monophosphate, HIFs; hypoxia-inducible factors, nitric oxide, IL-6, C-reactive protein, TNF alpha, prostaglandins)[7] which cause sensitization of perivascular nociceptors in the meninges or brain surface. If this happens repeatedly and continuously, it will cause chronic pain through central sensitization and cause spasm of the pericranial muscles which is felt as TTH.[1,6,7,8] The high frequency of TTH attacks can describe the high risk of various neuro-inflammatory processes such as cell edema, gliosis, excitotoxicity - mediated necrosis and other neuronal injury occurring in the brain. Neuronal cells that are damaged by this process affect the cognitive performance.[6,8,9]

Neuroimaging studies have reported that TTH patients have abnormal brain function, changes in the functional intensity and brain gray matter volume, disorders of the white matter tract system.[14] The decreased of gray matter volume, especially in brain structures that process pain, has been reported in chronic TTH, including cortex, anterior cingulate, insula, orbitofrontal cortex, parahippocampal gyrus and dorsal rostral pons are positively related to the duration and frequency of headache, suggesting that these structural changes are the consequence of central sensitization. The results of Wang et al study (2014) using functional magnetic resonance imaging (fMRI) and regional homogeneity (ReHo) analysis to identify the changes of spontaneous activity synchronization in 10 TTH patients and 10 healthy controls showed that compared to the healthy control group, the TTH group showed significantly lower regional homogeneity (ReHo) values in bilateral caudatus nucleus, precuneus, putamen, left medial frontal gyrus and superior frontal gyrus (p<0.005). These results indicate that in TTH patients there is a significant decrease in synchronization of neuronal activity in certain brain regions. The prequeneus region integrates sensation, cognition, and higher cortical activity to form awareness. The caudate

nucleus and putamen are the main components of the basal ganglia that play role in brain plasticity. In addition to their role in habit learning, action selection and motor control, the basal ganglia also regulate pain sensation, analgesic response, and transmission of various signals. The basal ganglia-thalamic-cortical loop system integrates many aspects where the basal ganglia also receive input from the cortex and subcortical. Because of the extensive connections in this loop system, abnormalities in pain processing in the basal ganglia can adversely affect other brain areas. Many studies have demonstrated functional changes of frontal lobes in various pain disorders such as fibromyalgia, and cluster headaches. TTH patients can also have frontal lobe functional abnormalities as in other pain disorders.[15] The decreased of gray matter volume due to long term changes in brain microstructure accompanied by multiple brain regions functional changes in TTH can result cognitive performance decline.

Table 2 also shows a significant correlation with a strong positive value between education and cognitive function scores (rho=0.493, p= 0.001), where the higher the level of education, the higher the MoCA-Ina score. In our study, high education level was defined by the level of senior high school/equivalent, diploma or bachelor's degree. Research by Wang et al (2020) which analyzed risk factors for cognitive decline in 257 epilepsy patients using mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA), clinical memory scale (CMS) showed that education level was correlated with cognitive test score ($p < 0.01$), with a significant difference between the junior high school and senior high school group ($p < 0.01$). The conclusion of the study was that high education level, good seizure control, AED monotherapy, and the absence of depression were protective variables against cognitive decline. The higher level of education, the lower cognitive impairment and education above the senior high school level appeared as a protective factor on cognitive function in epilepsy patients.[16] People with higher education levels have stronger ability to understand the instructions on cognitive function tests. In addition, patients with high education level are usually more understand about their disease and have better self-discipline, so they are more obedient to follow the strict treatment rules, with the consequence of increasing the treatment effectiveness and reducing cognitive decline.[16] Education can affect lifestyle, health behavior, social and economic interactions. Research has shown that improvements in brain function are also associated with changes in brain structure that are influenced by synaptic density, hippocampal volume and cortical thickness due to stimulation by learning processes during education.[17,18]

Table 2 shows a weak negative correlation between onset of epilepsy and cognitive score (rho= -0.225, p= 0.158), between seizure frequency and cognitive score (rho= -0.251, p= 0.114). Meanwhile, there was no significant relationship between age and cognitive score (rho= -0.182, p= 0.254). Although not statistically significant, based on table 1, the highest number of TTH subjects were in the onset of epilepsy >10 years group, especially in the TTH frequency category of episodic frequent (19.6%, 8 people) and chronic (24.4%, 10 people), which both of groups tend to have MoCA-Ina scores < 26 (abnormal). Likewise, TTH subjects in the high seizure frequency group (12-48 times/year) were higher than those in the lower seizure frequency group (<12 times/year). This is in accordance with the literature which states that the severity of epilepsy which includes long duration or onset, high intensity or frequency of seizures, polytherapy and drug-resistant epilepsy are associated with higher prevalence of TTH.[1,6] In our study, there was a significant correlation with moderate negative value between the TTH frequency category and cognitive function score, where the higher the TTH frequency category, the lower the MoCA-Ina score. So that indirectly, the onset of epilepsy and seizures frequency can still be related to cognitive function score even though in weak correlation.

Based on table 3, after controlling for age, the correlation between onset of epilepsy and cognitive score was getting weaker (rho= -0.109), while the correlation between seizure frequency and cognitive score was getting stronger (rho= -0.271) with a weak negative value. So age can still have an effect on cognitive function score even though there is no statistically significant correlation. This may be due to other factors that are more dominant in influencing cognitive function than age, such as the onset and frequency of seizures or TTH. For example, even though the age is older, if the onset of epilepsy is still new or the frequency of seizures or TTH is low, the

cognitive score can tend to be normal or vice versa. The weak correlation between onset of epilepsy and seizure frequency with cognitive score may also be influenced by the high education level in most of subjects (85.4%) in our study. Moreover, our study found a significant correlation with strong positive value between education and cognitive function score. It has also been described previously that high education level is one of protective variables against cognitive decline in epilepsy. [16]

The limitations of our study were the data of TTH frequency were collected by used a questionnaire form so that it relied on the patient's memory, the number of subjects was small (N 41), and the effect of anti-epileptic drugs on cognitive function was not evaluated.

CONCLUSION

Epilepsy is a chronic disease that increases the risk of interictal headaches, one of which is TTH.[1] The high frequency of TTH attacks can describe the high risk of various neuro-inflammatory processes that affect cognitive performance. In our study, there was a significant moderate correlation between the TTH frequency and cognitive function score in epilepsy patients. Population studies including the use of both headache diary and seizure diary are needed for further study.

ACKNOWLEDGMENTS

This research was supported by Dr Kariadi Hospital in Semarang, the Department of Neurology, Medical School, University of Diponegoro.

REFERENCES

1. Mainieri G, Cevoli S, Giannini G, Zummo L, Leta C, Broli M, et al. Headache in epilepsy: prevalence and clinical features. The Journal of Headache and Pain. 2015; 16 (72): 2-10
2. Sayed MA, Ibrahim HK, Bekhit AS, Thabit MN, Abdelmomen M. Clinical Characteristics of Headache in Egyptian Patients with Idiopathic Epilepsy. Journal of Behavioral and Brain Science. 2019; 9: 144-153
3. Wang X, Lang S, Zhang X, Zhu F, Wan M, Shi X, et al. Clinical factors associated with postictal headache in Chinese patients with partial epilepsy. Seizure. 2014; 23: 191–195
4. Cianchetti C, Dainese F, Ledda MG, Avanzini G. Epileptic headache: A rare form of painful seizure. Seizure 2017; 52: 169–75.
5. Özer G, Ünal Y, Kutlu G, Gömceli Y, İnan L. Prevalence of Interictal Headache in Patients with Epilepsy. Epilepsi. 2018; 24(2): 51-54
6. Nahid A, Hakimeh J. The Prevalence of Migraine and Tension Types of Headache among Epileptic Patients. Caspian J Neurol Sci. 2015; 1(3): 41-46
7. Britze J, Arngrim N, Schytz HW, Ashina M. Hypoxic mechanisms in primary headaches. Cephalalgia. 2016; 0 (0): 1–13
8. Mameniškienė R, Karmonaitė I, Zagorskis R. The burden of headache in people with epilepsy. Seizure. 2016; 41: 120-6
9. Lai TH, Protsenko E, Cheng YC, Loggia ML, Coppola G, Chen WT. Neural Plasticity in Common Forms of Chronic Headaches. Neural Plasticity. 2015; (1): 205985
10. Allendorfer JB, Arida RM. Role of Physical Activity and Exercise in Alleviating Cognitive Impairment in People With Epilepsy. Clin Ther. 2018; 40: 26–34
11. Witt JA, Helmstaedter C. Cognition in the early stages of adult epilepsy. Seizure. 2015; 26: 65–68
12. Leclezio L, Jansen A, Whittemore VH, de Vries PJ. Pilot Validation of the Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) Checklist. Pediatr Neurol. 2015; 52: 16-24
13. Anurogo D. Tension Type Headache. CDK. 2014; 41 (3): 186-191
14. Zhou J, Cheng S, Yang H, Lan L, Chen Y, Xu G, et al. The brain structure and function alterations in tension-type headache: a protocol for systematic review and meta analysis. Medicine. 2020; 99: 24
15. Wang P, Du H, Chen N, Guo J, Gong Q, Zhang J, et al. Regional homogeneity abnormalities in patients with tensiontype headache: a resting-state fMRI study. Neurosci Bull. 2014; 30 (6): 949–955
16. Wang L, Chen S, Liu C, Lin W, Huang H. Factors for cognitive impairment in adult epileptic patients. Brain Behav. 2020;10:1-11
17. Yu S, Wang X. Postictal headache in epileptic Patients. Molecular & Cellular Epilepsy. 2014; 1: e197

18. Wainsztein N, Lucci FR. Cortical Spreading Depression and Ischemia in Neurocritical Patients. Neurol Clin. 2017; 35: 655–664