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Research article

The effect of stress on the epilepsy recurrence

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Abstract

Epilepsy is a health problem that is both a medical problem and a social problem. This study aimed to determine the relationship between stress levels and recurrence rates in epilepsy patients at Dr Loekmonohadi Kudus Hospital. This research uses a descriptive correlation type of research, the approach method uses cross-sectional, the population in this study are all epilepsy patients and are registered in the medical record at Dr Loekmonohadi Kudus Regional Hospital in the period August 2023, there are 51 patients with a sample of 45 respondents. The measuring instrument used is the test. Spearman Rank Correlation. The results of the analysis showed a p-value of 0.094 > (α = 0.05). It can be concluded that Ha was rejected and Ho was accepted, so there is no relationship between stress levels and recurrence rates in epilepsy patients at Kudus Hospital in 2023.

INTRODUCTION

Epilepsy is a health problem that is both a medical problem and a social problem. It is a medical problem because epilepsy is a disease that requires close management and supervision in its treatment, while the psychosocial problems faced by epilepsy sufferers are greater than the medical problems they experience, where epilepsy patients are afraid that throughout their lives they will suffer from epilepsy. They are afraid to drive, afraid to swim, and the most frightening thing is having a seizure in public. Epilepsy is often associated with high injury rates, high death rates, bad social stigma, cognitive impairment and psychiatric disorders. Therefore, diagnosis needs to be paid attention to. Epilepsy is a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. We still do not know all mechanisms involved in the pathogenesis of epilepsy.[1]

The negative stigma that is developing in society regarding epilepsy is a challenge for the government and health practices. During current developments in science and technology, epilepsy is still considered a curse, contagious and incurable. This is one of the causes of increasing prevalence rates. Epilepsy cases have a prevalence of 6-10 per 100 population with an incidence reaching 50 per 100,000 population. With a population of more than 250 million people

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in Indonesia. In 2015, it is estimated that epilepsy sufferers will now reach 2.5 million people. The incidence of epilepsy in developed countries is found to be around 50 per 100,000 people, while in developing countries it reaches 100 per 100,000 people. Global data collection found 3.5 million cases per year, of which 40% are children and around 40% are adults and 20% are elderly.

There are two factors that trigger epilepsy, namely internal factors such as stress, fatigue, lack of sleep, menstrual cycle, and external factors such as excess alcohol, certain light, bathing. The production of free radicals has a role in the regulation of biological function, cellular damage, and the pathogenesis of central nervous system conditions. Epilepsy is a highly prevalent serious brain disorder, and oxidative stress is regarded as a possible mechanism involved in epileptogenesis.[2] Experimental studies suggest that oxidative stress is a contributing factor to the onset and evolution of epilepsy. Stress is an attempt by the body to adapt both physically and mentally to the surrounding conditions. If it cannot handle it, physical, behavioral and mental disorders will arise. Stress mediators such as corticotropin-releasing hormone, corticosteroids, and neurosteroids contribute to the pathogenesis of epilepsy. Factors that trigger epileptic seizures are in second place after drug withdrawal factors (40.9%), namely 31.3%.

Neurodegenerative diseases, such as Alzheimer's disease,Parkinson's disease, and amyotrophic lateral sclerosis, are defined by progressive loss of specific neuronal cell popula- tions and are associated with protein aggregates. A common feature ofthese diseases is extensive evidence ofoxidative and nitrosative stress (O&NS), which might be responsible for the dysfunction or death of neuronal cells which contributes to disease pathogenesis.[2] These neurodegenerative diseases affect distinct population groups: children, young adults, and the elderly. These diseases are much more prevalent in the elderly because of aging, environmental factors and to a lesser extent genetic factor. Treatments overlap between the two conditions as well. Antidepressants are the mainstays of treatment for both depression and anxiety disorders. Although benzodiazepines are effective in cases of acute anxiety or panic symptoms, treatment with an antidepressant is often viewed as more effective over the long term. A medicine such as alprazolam is an atypical benzodiazepine considered to be particularly effective for panic disorder, yet also has some antidepressant effect as well.[3]

Epidemiological data regarding stress as a risk factor for epileptic attacks is very useful in the management of epilepsy both in clinics and in the community. However, there has not been much research on this matter in Indonesia. Stress as a triggering factor for epileptic attacks is still controversial.[4] Epilepsy and depression share an unusually high coincidence suggestive of a common etiology. Disrupted production ofadult-born hippocampal granule cells in both disorders may contribute to this high coincidence. Chronic stress and depression are associated with decreased granule cell neurogenesis. Epilepsy is associated with increased production – but aberrant integration – of new cells early in the disease and decreased production late in the disease. In both cases, the literature suggests these changes in neurogenesis play important roles in their respective diseases. Aberrant integration of adult-generated cells during the development ofepilepsy may impair the ability ofthe dentate gyrus to prevent excess excitatory activity from reaching hippocampal pyramidal cells, thereby promoting seizures. Effective treatment of a subset of depressive symptoms, on the other hand, may require increased granule cell neurogenesis, indicating that adult-generated granule cells can modulate mood and affect. Given the robust changes in adult neurogenesis evident in both disorders,

competing effects on brain structure are likely. Changes in relative risk, disease course or response to treatment seem probable, but complex and changing patterns of neurogenesis in both conditions will require sophisticated experimental designs to test these ideas.[5] Therefore, the author is interested in examining the extent of the relationship between stress and attacks in epilepsy in Kudus, Indonesia.

METHODS

This research is a quantitative study using a associative quantitative design with a cross-sectional approach.[6] The sampling technique in this research used a purpose sampling technique. The population in this study were all epilepsy patients registered in the medical records at Dr. Loekmonohadi Kudus Regional Hospital. The benchmark researchers took in the period August 2023 was 51 patients.

The sample in this study was 45 respondents. The inclusion criteria were epilepsy patients who were fully recorded in the medical record, when studied, the respondent was fully conscious, willing to become a respondent by signing a research consent form (informed consent). Exclusion criteria were patients diagnosed with SNH (non-hemorrhagic stroke), research respondents who refused/canceled being respondents, respondents who did not fill out the questionnaire correctly or incompletely.

This study used a questionnaire containing a list of instructions for filling out, the identity of the respondent, the rate of recurrence in epilepsy patients, and stress levels which had been tested for validity and reliability using Pearson product moment correlation.The data in this study were analyzed using univariate and bivariate analysis. Univariate analysis was carried out on the variables age, gender, occupation, recurrence rate in epilepsy patients, and stress level. The bivariate analysis used was the Spearman rank correlation test analysis.

RESULTS

Based on table 1, it can be concluded that the average age of respondents is 37.13 years, the median respondent is 37 years. Most respondents were aged 30-39 years and the youngest was <20 years old while the oldest was >60 years old. Based on the prevalence of epilepsy in different studies and accounting for incomplete case identification the estimated number of children and adolescents in Europe with active epilepsy is 0.9 million (prevalence 4.5–5.0 per 1000), 1.9 million in ages 20–64 years (prevalence six per 1000) and 0.6 million in ages 65 years and older (prevalence seven per 1000). Approximately 20–30% of the epilepsy population have more than one seizure per month. Based on the age-specific incidence rates in European studies, the estimated number of new cases per year amongst European children and adolescents is 130 000 (incidence rate 70 per 100 000), 96 000 in adults 20–64 years (incidence rate 30 per 100 000) and 85 000 in the elderly 65 years and older (incidence 100 per 100 000). The proportion of both new and established cases with epilepsy in the young, adults and elderly in individual countries may differ substantially from total European distribution because of differences in age structure.[7]

The epilepsy patients in the Kudus were male with a total of 20 respondents (44.4%), while the female gender was 25 respondents (55.6%). In addition to suffering from the constant stress of living with this neurological condition, patients also frequently experience comorbid psychiatric and cognitive disorders which significantly impact their quality of life. There is growing appreciation that stress, in particular occurring in early life, can negatively impact brain development, creating an enduring vulnerability to develop epilepsy. This aligns with the solid connections between early life environments and the development of psychiatric conditions, promoting the

possibility that adverse early life events could represent a common risk factor for the later development of both epilepsy and comorbid psychiatric disorders. The influence of sex has been little studied, but recent research points to potential important interactions, particularly regarding effects mediated by HPA axis programming. Understanding these interactions, and the underlying molecular mechanisms, will provide important new insights into the causation of both epilepsy and of psychiatric disorders, and potentially open up novel avenues for treatment.[8]

The majority of epilepsy patients in the Kudus are employees with 20 respondents (44.4%), while the fewest are civil servants with 2 respondents (4.4%). In a recent study, investigators studied whether an acute, but serious,emotional life stressor could trigger the onset of epilepsy in patients with no history ofseizures. Though uncommon, out of over 4600 patients with epilepsy evaluated at an epilepsy patients reported severe emotional trauma as the onset of their epilepsy. Death of a loved one preceding an epileptic seizure accounted for 54% of these cases, while others included divorce, dissolution of a partnership, domestic abuse without head trauma, and job loss.[3]

The highest results obtained for the level of stress were in the very heavy category with 15 respondents (33.3%), while the lowest results were in the normal and mild categories with 5 respondents (11.1%). The pathophysiology of depression also involves the amygdala. Early positron emission tomography imaging noted increased activity in the amygdala in familial pure depressive disorder. Other subcortical brain regions are also involved in depression, such as the thalamus and caudate nucleus. A reverberating circuit has been proposed that involves underactive inhibitory networks, presumably GABAergic from the region of the caudate nucleus, which insufficiently prevents overactivation of the amygdala. The overactivation leads to anxiety symptoms that are excessive.[3]

The recurrence rate for epilepsy at Kudus was the highest with no seizures with 40 respondents (88.9%), while the lowest was with seizures with 5 respondents (11.1%). Anxiety is one of the common comorbid psychiatric disorders in epilepsy. Depression and anxiety are frequently comorbid in patients with epilepsy and exhibit bidirectional relationships.In this study, we also found a bidirectional relationship between depression and anxiety. Although depression had only direct effects on perceived stress, anxiety had both direct and indirect (via seizure control) effects. on perceived stress. According to previous studies, depressive and/or anxious mood is one of the seizure precipitants. One study with a longitudinal design used the PSS to show that perceived stress, along with anxiety and depression, was a significant predictor of seizure frequency. Some investigators suggested that a common mechanism that underlies depression, anxiety, stress, and epilepsy could be related to triggering seizures. Further study is needed to elucidate a causal relationship between depression, anxiety, and stress of epilepsy and mechanisms[9]. In epilepsy, individual seizures can be triggered by a variety of external and internal stimuli. One of the most common trigger factors reported by patients is stress. However prevalent, stress-related triggering of episodes seems underappreciated in epilepsy for various reasons, and its misinterpretation often leads to other diagnoses, e.g., psychogenic nonepileptic seizures (PNES) or normal reactions. This article illustrates the significant role of stress as a seizure-provoking factor by referring to nine patient narratives. From this perspective, it appears that there are characteristic patterns of stress triggering, e.g., stress-induced sleep disruption, forms of acute stress, or relaxation after stress. Sometimes seizures are mistaken as symptoms of stress. Patient narratives contain interesting clues relating

reports about stress and seizure histories to different epilepsy syndromes as well as nonepileptic episodes in a way that can strongly support the diagnostic process.[10]

Table 1
Frequency Distribution Based on Age Respondent

Indicators	f	%
Age		
<20 years	5	11,1
20-29 years	8	17,8
30-39 years	15	33,3
40-49 years	10	22,2
50-59 years	5	11,1
>60 years	2	4,4
Sex		
Male	20	44,4
Female	25	55,6
Occupation	n	%
Student	5	11,1
Employer	20	44,4
Entrepreneur	13	28,9
Farmer	5	11,1
Civil servant	2	4,4
Stress Level		
Mild	5	11,1
Moderate	10	22,2
Heavy	10	22,2
Very heavy	15	33,3
Epilepsy Recurrence		
Seizures	5	11,1
Non-Seizures	40	88,9
Total	45	100,0

Table 2 shows that of the 45 respondents with stress levels in the normal category, 5 (100%) had seizures. from the stress level of the mild category with no seizures as much as 1 (20%), seizures as many as 4 (80%), from the moderate stress level with no seizures as many as 4 (40%), seizures as many as 6 (60%), from the stress level category severe with seizures as many as 10 (100%), while the stress level is in the very severe category with seizures as many as 15 (100%). Stress can influence epilepsy inmultipleways. A relation between stress and seizures is often experienced by patientswith epilepsy. Numerous questionnaire and diary studies have shown that stress is the most often reported seizure-precipitating factor in epilepsy. Acute stress can provoke epileptic seizures, and chronic stress increases seizure frequency. In addition to its effects on seizure susceptibility in patients with epilepsy, stress might also increase the risk of epilepsy development, especially when the stressors are severe, prolonged, or experienced early in life. Although the latter has not been fully resolved in humans, various preclinical epilepsy models have shown increased seizure susceptibility in naïve rodents after prenatal and early postnatal stress exposure. In the current review, we first provide an overview of the effects of stress on the brain. Thereafter, we discuss human as well as preclinical studies evaluating the relation between stress, epileptic seizures, and epileptogenesis, focusing on the epileptogenic effects of early life stress. Increased knowledge on the interaction between early life stress, seizures, and epileptogenesis could improve patient care and provide a basis for new treatment strategies for epilepsy [11].

The results of statistical tests using the Spearman test obtained a p value of 0.094 > (α = 0.05) and a correlation coefficient value of 0.253. These results show that there is no relationship between the level of stress and the level of recurrence in epilepsy patients because the p-value is 0.094 > (α = 0.05), with the strength of the relationship being weak because the correlation coefficient value (0.253) is in the range 0.20-0.399 and has a positive relationship direction, meaning that the higher the respondent's stress level, the higher the epilepsy recurrence rate and vice versa, the lighter the stress level, the lighter the epilepsy recurrence rate.

Table 2
The Relationship between Stress and Recurrence of Epilepsy in Kudus

Stress Level	Recurrence				Total		*Correlation coeffisient*	p
	Seizures		Non-Seizures					
	f	%	f	%	f	%		
Normal	0	0,00	5	11,11	5	11,11		
Mild	1	2,22	4	8,89	5	11,11		
Moderate	4	8,89	6	13,33	10	22,22	*0.253*	0,094
Heavy	0	0,00	10	22,22	10	22,22		
Very Heavy	0	0,00	15	33,33	15	33,33		
Total	5	11,11	40	88,89	45	100,00		

DISCUSSION

The results of the study showed that there was no relationship between stress levels and recurrence rates in epilepsy patients at the Kudus. Of the 45 respondents, stress levels were in the normal category with no seizures, 5 respondents (100%), mild stress levels occurred more frequently in those who did not have seizures. 4 respondents had seizures (80%), moderate levels of stress occurred more frequently in those who did not have seizures, 6 respondents (60%), severe stress levels occurred more in those who did not have seizures, 10 respondents (100%), very severe levels of stress occurred. more in those who did not have seizures, 15 respondents (100%). Statistical results using the Spearman rho test obtained a p value of 0.094 (>0.05), so Ho was accepted, which means there is no relationship between stress levels and recurrence rates in epilepsy at the Kudus.

Epilepsy is a health problem that is both a medical problem and a social problem.[12] It is a medical problem because epilepsy is a disease that requires close management and supervision in its treatment, while the psychosocial problems faced by epilepsy sufferers are greater than the medical problems they experience, where epilepsy patients are afraid that throughout their lives they will suffer from epilepsy. They are afraid to drive, afraid to swim, and the most frightening thing is having a seizure in public. Epilepsy is often associated with high injury rates, high death rates, bad social stigma, cognitive impairment and psychiatric disorders. Therefore, it is necessary to pay attention to establishing a diagnosis.[13]

The negative stigma that is developing in society regarding epilepsy is a challenge for the government and health practices in particular. In the midst of current developments in science and technology, epilepsy is still considered a curse, contagious and incurable. This is one of the causes of increasing prevalence rates.[5]

There are two factors that trigger epilepsy, namely internal factors such as stress, fatigue, lack of sleep, menstrual cycle and external factors such as excess alcohol, certain light, bathing. Stress is an attempt by the body to adapt both physically and mentally to the surrounding conditions, if it cannot overcome it, physical, behavioral and mental disorders will arise. Stress mediators such as corticotropin-releasing hormone, corticosteroids, and neurosteroids contribute to the pathogenesis of epilepsy. Preclinical studies clearly show that early life stress predisposes the brain to provoked seizures and to later epilepsy. For example, if pregnant female rodents are stressed (eg, by restraint, bright lights or injections), it is easier to induce seizures several weeks later in the pups in response to kindling, audiogenic stimuli and chemoconvulsants. Similarly, postnatal stress induced by separation of pups from their mother renders them more susceptible to later seizures, with kindling and chemoconvulsants.[12] Mitochondrial oxidative stress and dysfunction are contributing factors to various neurological

disorders. Recently, there has been increasing evidence supporting the association between mitochondrial oxidative stress and epilepsy. Although certain inherited epilepsies are associated with mitochondrial dysfunction, little is known about its role in acquired epilepsies such as temporal lobe epilepsy (TLE). Mitochondrial oxidative stress and dysfunction are emerg- ing as key factors that not only result from seizures but may also contribute to epileptogenesis. The occurrence of epilepsy increases with age, and mitochondrial oxidative stress is a leading mechanism of aging and age-related degenerative disease, suggesting a further involvement of mitochondrial dysfunction in seizure generation. Mitochondria have critical cellular functions that influence neuronal excitability including production of adenosine triphosphate (ATP), fatty acid oxidation, control of apoptosis and necrosis, regulation of amino acid cycling, neurotrans- mitter biosynthesis, and regulation of cytosolic Ca2+ homeostasis. Mitochondria are the primary site of reactive oxygen species (ROS) production making them uniquely vulnerable to oxidative stress and damage which can further affect cellular macromolecule function, the ability of the electron transport chain to produce ATP, antioxidant defenses, mitochondrial DNA stability, and synaptic glutamate homeostasis. Oxidative damage to one or more of these cellular targets may affect neuronal excitability and increase seizure susceptibility. The specific targeting of mitochondrial oxidative stress, dysfunction, and bioenergetics with pharmacological and non- pharmacological treatments may be a novel avenue for attenuating epileptogenesis.[14] In the chronic phase of epilepsy, neurogenesis may drop below normal levels. While reduced neurogenesis alone does not appear sufficient to cause depression, it could be a risk factor. Moreover, disruption of the neurogenic niche in the epileptic brain may limit the utility of antidepressant treatments, just as radiation treatment limits the utility of fluoxetine in rodents. Studies have yet to be conducted to determine whether depressed temporal lobe epilepsy patients with hippocampal sclerosis respond differently to antidepressive therapy relative to epileptic patients without obvious hippocampal damage. A recent study ofdepressive behavior in rodents rendered epileptic using the pilocarpine model (which produces significant cell loss) however, found fluoxetine to be ineffective. Such studies in humans could provide important guidance for the treatment of depression in patients with epilepsy.[5,15,16]

CONCLUSION

Characteristics of respondents in terms of age, the highest age level was found to be between 30-39 years with a total of 15 respondents (33.3%). The gender found most often was female with 25 respondents (55.6%). Most of the jobs obtained were employees with 20 respondents (44.4%). The highest number of stress levels obtained was in the very severe category with 15 respondents (33.3%). The highest rate of recurrence obtained was in the non-seizures category with 40 respondents (88.9%). There is no relationship between the level of stress and the level of recurrence in epilepsy patients at Kudus because the p-value is 0.094 > (α = 0.05), with the strength of the relationship being weak because the correlation coefficient value (0.253) is in the range of 0.20 -0.399 and has a positive relationship direction, meaning that the higher the respondent's stress level, the higher the epilepsy recurrence rate and vice versa, the lighter the stress level, the lighter the epilepsy recurrence rate.

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CONFLICTS OF INTEREST

Neither of the authors has any conflicts of interest that would bias the findings presented here.

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