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OSTEOPENIA IN MALE AND FEMALE PATIENTS USING CARBAMAZEPIN AND VALPROIC ACID COMBINATION THERAPY: ANALYSIS OF PREVALENCE AND ITS RELATIONSHIP WITH EPILEPSY CHARACTERISTICS

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ABSTRACT

Background : Epilepsy is a chronic condition with unprovoked seizures. One of the changes affected by anti-epileptic drugs is a decrease in bone density. Gender and sex hormones have implications on bone density. **Objective :** To determine the prevalence difference osteopenia between male and female, and relationship with clinical characteristics epilepsy patients taking a combination of carbamazepine and valproic acid. **Methods:** A cross-sectional study with 22 epileptic patients with age range of 18-60 years taking combination of carbamazepine and valproic acid at the Neurology Department Dr. Kariadi Semarang during June to October 2021 who met the inclusion and exclusion criteria. Patient data were obtained by filling out a questionnaire. The assessment of osteopenia was carried out by examination of Bone Mineral Densitometry. Data analysis was using Chi Square test and Spearman correlation test. The result was determined to be significant if the p value <0.05. **Results :** There were 11 male subjects and 11 female subjects. Chi Square resulted in significant difference between male and female ($p<0.05$). Spearman correlation test showed a relationship between osteopenia and duration before combination therapy, for men rho 0.734 ($p<0.05$), women rho 0.786 ($p<0.001$). There was a relationship between osteopenia and the onset of epilepsy, male rho 0.603 ($p<0.05$), female rho 0.757 ($p<0.001$). There was a relationship between osteopenia and age, male rho 0.487 ($p=0.129$), female rho 0.780 ($p<0.001$). There was also a relationship between osteopenia and seizure frequency, male rho 0.457 ($p<0.05$), female rho 0.467 ($p=0.026$). **Conclusion:** There was a significant osteopenia prevalence difference between male and female epilepsy patients taking combination of carbamazepine and valproic acid. Moderate and strong relationship were found between osteopenia and clinical characteristics epilepsy.

Keywords : *Epilepsy, osteopenia, carbamazepine, valproic acid*

BACKGROUND

Epilepsy is the most common chronic neurological condition, affecting about 50 million people worldwide. One of the metabolic changes affected by OAE is bone metabolism, accompanied by a reduction in bone mineral density and an increased risk of fracture. This is particularly unfavorable for people with epilepsy, as they already have a predisposition to fractures due to side effects of other drugs (eg ataxia), pre-existing neurological deficits (eg cerebral palsy) and falls due to seizures[1,2].

Carbamazepine induces cytochrome P450 and reduce vitamin D levels. Long-term use of carbamazepine causes bone loss, induces a decrease in bone and mineral metabolism and decreases Bone Mineral Density (BMD). It has also been found that serum calcium and estrogen levels are found to be lower in women with epilepsy who take carbamazepine in the premenopausal phase. Valproic acid is an antiepileptic that suppresses cytochrome P450, showing significant effects on bone growth and metabolism. Previous studies have shown that valproic acid directly affects bone growth[2].

Epilepsy in women plays a different role related with regarding bone density. Other factors also able to modulate bone density such as sex hormones, menopause, where gender-specific implications have implications for bone density[3].

Dr. Kariadi Hospital is a referral hospital where epilepsy patients were referred from regional hospitals who have taken anti-epileptic drugs and they were combination drug therapy with carbamazepine and valproic acid.

METHODS

This study is a cross-sectional study, which was conducted at the outpatient polyneuropathology of Dr Kariadi Hospital Semarang from June to October 2021. The subjects of this study were

epilepsy patients who received a combination of carbamazepine and valproic acid aged 18-60 years. Meanwhile, the exclusion criteria for patients with epilepsy were absenteeism, menopause, and long-term use of corticosteroids.

This research has received permission from the Ethics Committee of the Faculty of Medicine UNDIP with number 802/EC/KEPK-RSDK/2021. Patients were selected based on inclusion and exclusion criteria, then informed consent was given to the patient. The study began by taking a history. Then the patient was examined for Bone Mineral Densitometry at the Radiology Installation of Dr Kariadi Hospital.

The data were processed using the SPSS Statistics for Windows version 26 program. To determine the difference in the prevalence of osteopenia in male and female epileptic patients using a combination of carbamazepine and valproic acid, a Chi-square test was performed. The confounding variables, namely the length of therapy before the combination, the duration of combination therapy, the frequency of seizures, age and onset of epilepsy will be subjected to a bivariate test with the Spearman correlation test. Then a partial correlation test will be carried out by controlling for age, seizure frequency and sun exposure. The results are said to be meaningful if $p < 0.05$.

RESULTS

Table 1. Characteristics of Research Subjects

Variable	F			Mean	
	Total	Man	Woman	Man	Woman
DEMOGRAPHICS					
Gender					
Males	11 (50%)				
Females	11 (50%)				
Age (years)				30,9 ± 6,31	30,18 ± 8,37
CLINICAL					
Duration of therapy (years)*				4,82 ± 5,56	11,9 ± 9,93
Combination therapy duration				2,36 ± 0,8	3,36 ± 1,2
Epilepsy onset (years)				8,09 ± 7,82	13,81 ± 11,12
Seizure frequency/ years				51,1 ± 43,8	89,27 ± 48,13
Sun exposure		8 (72,7%)	9 (81,8%)		
Not exposed	17 (77,3%)	3 (27,3%)	2 (18,2%)		
Exposed	5 (22,7%)				
Bone density					
Normal	13 (59,1%)	9 (81,8%)	4 (36,3%)		
Osteopenia	9 (40,9%)	2 (18,2%)	7 (63,7%)		

* duration of AED therapy before combination therapy

Based on Table 1 above, it shows that the mean age of epilepsy patients who use combination therapy of carbamazepine and valproic acid were mostly young adults, the mean age of women was higher than that of men. The mean duration of therapy before combination therapy, the mean duration of combination therapy and the mean onset of epilepsy were also higher in women. The mean frequency of seizures also showed that women had experience seizures more often than men. The number of subjects exposed to sunlight was more in men than women. The number of subjects with osteopenia showed more women than men.

Table 2. Differences in osteopenia in male and female epilepsy patients

Variable	Bone Density		p
	Normal	Osteopenia	
Gender			
Males	9 (81,8 %)	2 (18,2 %)	*0.040
Females	4 (36,3%)	7 (63,7 %)	

** Chi-Square is significant if p<0.05*

Table 2 shows that osteopenia were more common in female patients, namely 7 patients (63.7%) compared to 2 male patients (18.2%) and showed a significant difference (p=0.040).

Table 3. Relationship of Osteopenia with duration of OAE** therapy, duration of combination therapy, onset of epilepsy, age and frequency of seizures in male and female patients.

Variable	Males		Females	
	rho	p	rho	p
Duration of therapy**	0.734	0.01*	0.786	0.004*
Epilepsy onset	0.603	0.04*	0.757	0.007*
Age	0.487	0.129	0.780	0.005*
Seizure frequency***	0.457	0.015*	0.469	0.026*
Combination therapy duration	1.000	0.001*	0.880	0.001*

* Spearman Correlation Test is significant if p<0.05
** Duration of therapy: duration of OAE therapy before combination therapy
*** Frequency of seizures per year

Table 3 showed that rho of the duration of therapy before combination therapy and the onset of epilepsy had a strong significant relationship with osteopenia were higher in the female group than in the male group. Age had a significant relationship with osteopenia in the female group (p = 0.005) with a rho value of 0.780 which indicated the strength of a strong relationship, while in the male group it was not significant.

The frequency of seizures with osteopenia in both groups showed a moderately significant association. The duration of combination therapy has a strong and significant relationship with osteopenia with higher rho in the male group than in the female group.

Table 4. Relationship of Osteopenia with duration of therapy*** by controlling for age, seizure frequency and sun exposure in male and female epilepsy patients

Variable	Control Variable	Males		Females	
		rho	p	rho	p
Duration of therapy***	Before controlled	0.734	0.01*	0.786	0.004*
	After controlled				
	Age	0.880	0.001*	0.683	0.029*
	Seizure frequency**	0.926	0.001*	0.814	0.004*
	Sun exposure	0.937	0.001*	0.683	0.029*

* Partial Correlation Test is significant if p<0.05
** Frequency of seizures per year
*** Duration of OAE therapy before combination therapy

Table 4 showed rho male were higher than female group, indicating that age, seizure frequency and sun exposure has a strong influence on women and weak on men, so that after controlling, the strength of the relationship is still strong.

Tabel 5. Relationship of Osteopenia with epilepsy onset by controlling for age, seizure frequency and sun exposure in male and female patients

Variable	Control Variable	Males		Females	
		rho	p	rho	p
Epilepsy onset	Before controlled	0.603	0.04*	0.757	0.007*
	After controlled				
	Age	0.813	0.004*	0.211	0.558
	Seizure frequency**	0.721	0.019*	0.750	0.012*
	Sun exposure	0.759	0.011*	0.655	0.040*

* Partial Correlation Test is significant if p<0.05
** Frequency of seizures per year

Table 5 showed relationship were still strong and significant in both groups, indicating that age, seizure frequency and sun exposure had a significant effect, so that after being controlled, the strength of the relationship was still strong. The exception was when age was controlled for women the relationship was not significant.

Table 6. The relationship between Osteopenia and duration of combination therapy by controlling for age, seizure frequency and sun exposure in male and female epilepsy patients

Variable	Control Variable	Males		Females	
		rho	p	rho	p
Combination therapy duration	Before controlled	1.000	0.01*	0.880	0.001*
	After controlled				
	Age	1.000	0.001*	0.746	0.013*
	Seizure frequency**	1.000	0.001*	0.904	0.001*
	Sun exposure	1.000	0.001*	0.883	0.001*

* Partial Correlation Test is significant if p<0.05
** Frequency of seizures per year

Table 6 showed male's rho were higher than female, indicating that age, seizure frequency and sun exposure did not had an influence on males, so that after age, seizure frequency and sun exposure were controlled, the strength of the relationship was still strong.

In female subjects, the relationship between osteopenia and duration of combination therapy showed that age had a strong influence, whereas seizure frequency and sun exposure showed a weak effect, but the relationship was still strong .

DISCUSSION

Based on Table 1 shows that the number of male research subjects compared to women is the same. The prevalence of epilepsy between men and women is not much different. The prevalence of epilepsy tends to increase with age, peaking in young adults. The number of subjects exposed to the sun is more in men than women, this is because men have more work in open spaces than women[4,5,6].

Table 2 shows that osteopenia is more common in female patients. Estrogen deficiency plays an important role in bone metabolism and the development of osteopenia for both sexes and is more pronounced in women and at a younger age than in men. Anti-epileptic drugs that induce cytochrome P450 enzymes will reduce estradiol levels in women. In accordance with the study of Alison M. Pack et al in the United States in 2011 which examined 115 pre-menopausal female epilepsy patients, it was found that patients taking anti-epileptic drugs that induce cytochrome P450 enzymes, namely carbamazepine and phenytoin, had lower estradiol levels compared to the group of epilepsy patients receiving taking non-inducer anti-epileptic drugs[7].

Men have higher bone density in the femur and higher bone mineral content in the lumbar vertebrae. Women begin to lose bone at an earlier age and at a faster rate than men. Women in their 50s have four times the rate of osteoporosis and twice the rate of osteopenia, and tend to fracture 5 - 10 years earlier than men. This is also influenced by physical activity and sun exposure which is relatively higher in males[8].

This is in accordance with Selma Cvijetic Avdagic's study in Croatia in 2018 which examined 51 men and 75 women, evaluating bone density in the lumbar vertebrae, femur and distal radius using DXA. Bone density was higher in males at the 3 sites measured compared to females, with males reaching peak density later than females, particularly in the lumbar vertebra[9].

Table 3 showed that the incidence of osteopenia increased along with the duration of consumption of antiepileptic drugs, both in men and women. The longer patients take anti-epileptic drugs was directly proportional to the frequency of occurrence of osteopenia in epilepsy patients. This is consistent with the theory that antiepileptic drugs that induce cytochrome P450 enhance the performance of enzymes responsible for vitamin D metabolism, resulting in the conversion of 25(OH) vitamin D to inactive metabolites. This conversion results in a decrease in 1,25(OH)2 vitamin D leading to decreased calcium absorption, with secondary hyperparathyroidism, respectively, increased bone resorption and accelerated bone loss[2]. Meanwhile, anti-epileptic drugs that inhibit cytochrome P450, in this study valproic acid, had a direct effect on bone cells, acting as HDAC (Histone Deacetylase) inhibitors. In osteoblastic-like cells, valproic acid promotes cell proliferation and pre-osteoblast differentiation through the induction of the Runx2 gene, which plays an important role in osteoblast differentiation and is negatively regulated by HDAC. Valproic acid significantly decreases the synthesis of two bone proteins, collagen type 1 and osteonectin, which suggest an important role in bone formation and subsequent mineralization by mature osteoblasts. Type 1 collagen is a major protein component of the bone matrix and mutations in type 1 collagen chains 1 and 2 are the cause of osteogenesis imperfecta in the majority of cases, whereas osteonectin is a collagen-binding glycoprotein, which is important for the maintenance of bone mass and normal bone remodeling[10].

The statement that prolonged consumption of anti-epileptic drugs will reduce bone density values is supported by several studies, notably that conducted by Enra Mehmedika Suljic et al in 2018 in Sarajevo, Bosnia with 50 young adult epilepsy patients with carbamazepine monotherapy, revealing that the most effective epilepsy treatment performed for more than 1 year resulted in low bone density ($p=0.031$)[11]. The same statement was also obtained in a study conducted by Cigdem Ecevit et al ($p<0.05$) and Sook Hui Kim et al. who studied 33 epilepsy patients aged 18-50 years in Korea who showed low bone density in epilepsy patients taking the antiepileptic drug carbamazepine. more than 6 months ($p=0.043$)[12,13]. In another study conducted by Simona Alexandra Beniczky et al conducted in Denmark, it was stated that the duration of anti-epileptic drug therapy had a significant relationship with low bone density ($p<0.05$)[14].

Table 3 also showed that the longer the onset of epilepsy, the higher the frequency of occurrence of osteopenia in both groups. This is possible because the longer the onset of epilepsy, the relatively longer consumption of antiepileptic drugs. Rho was found to be higher in female subjects, this could be due to the more prominent effect of estrogen in women. In a study conducted by Josephine Swanton et al in England in 2007, examining bone density in 208 epilepsy patients found a significant association of low bone density with epilepsy onset ($p<0.01$)[15].

In Table 3 it can also be seen that in female subjects the older the age of epilepsy patients will increase the frequency of occurrence of osteopenia. This could be because age is one of the main risk factors for osteopenia. Age can affect bone density through deficiency of sex hormones that play an important role in bone density, secondary hyperthyroidism, increased bone marrow fat, and decreased physical activity. Sex hormone deficiency will increase the occurrence of osteopenia. In male subjects, there was no significant relationship between osteopenia and age. This is because men will experience a decrease in density at an older age than women[8,16].

Based on Table 3 it can also be concluded that the higher the frequency of seizures increased the frequency of occurrence of osteopenia in both

male and female subjects. Seizures will cause damage to brain cells and also affect hormones and cytokines in epilepsy patients. There is a complex bidirectional interdependence between sex steroid hormones and epilepsy; hormones affect seizures, while seizures affect hormones so that they interfere with reproductive endocrine function. Both female and male sex steroid hormones affect brain arousal. Sex hormone deficiency and increased proinflammatory cytokines will increase the incidence of osteopenia. This is in accordance with a study conducted by Mikiko Yamada in Japan in 2013 which examined 161 epilepsy patients, which found a significant relationship between seizure frequency and changes in bone metabolism ($p<0.05$)[17,18].

Based on Table 3, it can also be concluded that the longer consumption of combination anti-epileptic drugs increased the frequency of occurrence of osteopenia in both male and female subjects. Rho was found to be higher in male subjects because women will begin to experience a decrease in bone density at an earlier age than men. Administration of combination antiepileptic drugs will increase the risk of developing low bone density. According to a study conducted by G. Farhat et al in 2002 in Lebanon in 71 epilepsy patients who took antiepileptic drugs for at least 6 months, namely phenytoin, carbamazepine, phenobarbital, valproic acid, clonazepam, gabapentin, topiramate and lamotrigine. In this study, there was a significant difference where epilepsy patients with polytherapy had lower bone density than patients with monotherapy ($p<0.05$)[19].

Table 4 showed that the relationship between osteopenia and duration of therapy before the combination by controlling for age, in the group of women, age has a strong influence, this is because the age of women is closely related to a decrease in estrogen. Whereas in male subjects, age has a weak influence, this is because men will experience a decrease in bone density at an older age. Sun exposure has a strong effect on female subjects and weak influence on male subjects, this is because sunlight functions on vitamin D metabolism so that it affects bone density[19,20].

CONCLUSION

Combination of carbamazepine and valproic acid had the effect of reducing bone density. Gender and sex hormones were strongly affect the incidence of osteopenia. We found that the prevalence of osteopenia is significantly different between women than men. And there is a strong and significant relationship between osteopenia and duration of therapy before combination, duration of combination therapy, onset of epilepsy, age and frequency of seizures.

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