Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.279212.3278 Volume 31, Issue 1.1, JAN. 2025, Supplement Issue
Manuscript id ZUMJ-2403-3278
Doi 10.21608/ZUMJ.2024.279212.3278
Original Article

Serum Orexin in Epilepsy: Relation to Cognitive Impairment and Sleep Disorders

Rania Y. Helal[1], Amany M. AbdAllah[2], Sabah E. Fathy[1*], Noha A. Hashim[1]
[1]Department of Neurology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Department of family medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding Author:
Sabah Elsayed Fathy

E-mail:
drsabah85@yahoo.com

Submit date 26-03-2024
Revise date 23-04-2024
Accept date 26-04-2024

ABSTRACT

Background: Epilepsy has many co-morbidities which may disturb patient life more than the seizures themselves. Seizures can change the brain both structurally and functionally, manifesting as cognitive and neuropsychological disorders. Roughly 30–40% of epileptic patients suffer from cognition changes. Frequent abnormal neuronal discharge, especially status epilepticus, causes oxidative stress leading to disruption of cognitive function. **Methods:** This case control study was conducted on 158 epileptic patients and158 apparently healthy individuals as a control group, all individuals were exposed to cognitive function testing via The Montreal Cognitive Assessment, sleep quality assessment by Pittsburgh Sleep Quality Index and evaluation of the serum level of orexin was done. **Results:** 62% of epileptic patients had cognitive impairment; the best cutoff of orexin in prediction of poor cognition among PWE is ≤195 with sensitivity 85.7%, specificity 91.7%. **Conclusions:** Our data concluded that the prevalence of cognitive impairment in epilepsy is high; serum orexin level could be used as a predictor for cognitive impairment and sleep disorders in epileptics.
Keywords: Orexin, epilepsy; cognitive impairment; sleep disorders.

INTRODUCTION

Epilepsy is one of the most common brain disorders characterized by transient, unexpected, and uninhibited episodes of brain dysfunction resulting in motor, sensory or behavioral symptoms. It affects nearly 65 million people worldwide **[1].**

Epilepsy has much co-morbidity which may disturb patient life more than the seizures themselves **[2].** Seizures can change the brain both structurally and functionally, manifesting as cognitive and neuropsychological disorders.

Approximately 30–40% of patients with epilepsy (PWE) suffer from cognition changes **[3]**. Frequent abnormal neuronal discharge, especially status epilepticus, cause oxidative stress; change synaptic connection of neurons, neuronal death, mainly in the hippocampus or entorhinal cortex, which is closely associated to interrupting the continuity of synapses and disturb cognitive process **[4].**

The reciprocal relationship between sleep and epilepsy had been documented as one of the main risk factors for the probability of having seizures again is sleep disturbance. **[5]**. Furthermore, the circadian rhythm itself appears to impact the timing and the severity of epileptic seizures **[6].** On the other hand, sleep macro- and microstructure alterations are linked to epilepsy **[7].** Given that epilepsy is a complex, multidimensional illness involving underlying pathology, neuropsychiatric and sleep co-morbidities, and the impact of both pharmacological and non-pharmacological therapies, these changes are multifactorial **[8].** Apart from these numerous factors, research indicates that epileptic activity directly affects sleep architecture, continuity, and oscillations.

Orexin (OX) is not a single protein, but two peptides which are secreted by specific neurons in the lateral hypothalamus **[9].** Orexin or orexin peptides are two neuropeptides, orexin A (OXA) and orexin B (OXB), acting widely on the central and peripheral system, controlling feeding, sleep cycle, metabolism, neuroendocrine and immune functions **[10].**

OXs and its receptors were found to be involved in the regulation of multiple pathological processes predominantly in neurological disorders. Harada et al. reported improvement of

the nerve injury following intracerebroventricular injection of OXA in a cerebral ischemia model in mice **[11].** Xiong et al. reported that OXA can inhibit inflammation after cerebral ischemia in rats by reducing the mRNA expression of TNFα and IL-6 **[12].** Through a series of molecular events, dysfunction of orexin signaling can lead to diseases such as epilepsy and other sleep disorders **[13].**

Hypocretin/orexin neurons (HONs) release several excitatory transmitters, including Hypocretin/orexin peptides and glutamate **[14].** HONs are proposed to exacerbate epileptic seizures, in part because of their reciprocal connections with brain regions involved in epileptogenesis, such as the hippocampus, through connections monosynaptic and polysynaptic. **[15].**

This also suggests that orexin may be involved in the process of epileptogenesis, as application of OX-A (Orexin-A) to hippocampal slices modulated the balance between neurotransmitters GABA-ergic (gamma-aminobutyric acid) and glutamatergic neurons. **[16, 17].**

Recently, Orexin receptor antagonists (ORAs) have been gaining more and more attention as a new treatment for seizures. Orexin was discovered in the early 2000s and has since been widely accepted as a key sleep modulator. Sleep has long been known to play a major role in seizures and epilepsy **[18].**

It is thought that the circadian rhythm is essential for the formation and consolidation of memory in the hippocampus, which controls a variety of physiological processes, such as cognitive performance and memory **[19].** If the circadian rhythm is disrupted, it can lead to a decrease in the clearance of Aβ and tau, which is a microtubule-related protein in the brain's glymphatic system **[20].** An increase in local brain oxidative stress and a decrease in circulating melatonin levels can lead to cognitive dysfunction and increase the risk of Alzheimer's disease (AD) **[21]**.

Several lines of evidence indicate that orexin contributes to attentional processing and learning via actions on the medial prefrontal cortex, cholinergic system in the basal forebrain, dopaminergic neurons in the ventral midbrain, and noradrenergic neurons in the LC **[22].** This study aimed to analyze the association of serum Orexin-A level, as a new serum biomarker, with cognitive function and sleep disorders in epileptic patients.

METHODS

Subjects included in the study: This case control comparative study was carried out in the Epilepsy Clinic Neurology Department, Faculty of Medicine, Zagazig University Hospitals in the period from march to October 2023. Total 158(91 male and 67 female with their age 32.2±8.26) patients were diagnosed with idiopathic epilepsy according to EEG, and met the diagnostic guidelines of international league against epilepsy with exclusion of the following; patients with secondary causes of epilepsy as CNS infections, head trauma, metabolic encephalopathy, electrolyte disturbance, brain tumor, patients with system failure or malignancies, and patients with severe intellectual disability that can hinder scale application.

Additionally, 158 healthy individuals who received physical examination in the hospital during the same time were enrolled into the control group,

Study tools: All patients were subjected to complete history taking stress on age of onset of illness, type of seizure, frequency, and history of status epilepticus were collected.

The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the quality of sleep over the course of the previous month. Sleep latency, length, disturbance, daytime dysfunction, habitual sleep efficiency, subjective sleep quality, and usage of sleep drugs are the seven component subscales that are covered by its 19 questions. The whole score arrays ranging from 0 to 21. Higher scores correspond to lower sleep quality, with a threshold of ≥8 considered to be poor sleep **[23].** The Suleiman et al. **[24]** Arabic version was utilized, with a Cronbach's α of 0.74.

The Montreal Cognitive Assessment (MoCA) was conducted for patients and control groups to evaluate the following cognitive domains visuospatial/executive functions, naming, memory, attention, language, abstraction and orientation. Those with total MoCA score less than 26 will be diagnosed as Cognitive impairment **[25].**

Sample acquisition and testing

Venous blood (5 mL) was acquired from each participant in the two groups at admission, followed by 10-min centrifugation (24°C, 3000 rpm) to acquire serum. The Orexin-A was quantified by Enzyme-linked immunosorbent assay with kits (Peninsula Laboratories, Inc. Belmont, CA, USA), under strict guidelines.

The Institutional Review Board, Faculty of Medicine Zagazig University approved this study (ZU-IRB #11366/10-12-2023). The study was done according to the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

STATISTICAL ANALYSIS

Version 26 of the SPSS (Statistical Package for the Social Sciences) program was used to analyze the data. The chi square test was used to compare categorical variables, and their absolute frequencies were used to describe them. In order to validate assumptions for use in parametric testing, the Kolmogorov-Smirnov test was employed. Depending on the type of data, the means and standard deviations or the median and interquartile range were used to characterize quantitative variables. The independent sample t test (for regularly distributed data) and the Mann Whitny test (for non-normally distributed data) were used to compare quantitative data between two groups. The degree and direction of the correlation between two variables were evaluated using the Spearman rank correlation coefficient. A ROC curve was employed to ascertain the best cutoff value. The level statistical significance was set at $P<0.05$. A highly significant difference was present if $p\leq0.001$.

RESULTS

This study included 158 PWE and 158 healthy controls. There is statistically non-significant difference between groups regarding age, gender, education, smoking, residence or family history of neurological diseases, while a statistically significant difference between groups regarding Orexin level and total PSQI score. As regard disease-specific data, median frequency of seizures per month was three/month (IQR; 1 to 5 times/month). About 80% had GTC type of epilepsy and median disease duration was 14 years. Larger percentage of patients received polytherapy (64.6%) table (1). There is statistically significant difference between groups regarding visuospatial, naming, attention, language, abstraction, recall, orientation and total MOCA score (all were significantly higher among PWE). At cutoff≥27, patients can be classified as having normal cognition which represents 38% among PWE versus 100% among control group with statistically significant difference table (2).

Table (3) showed that there is statistically non-significant relation between cognitive function among PWE and age, BMI, smoking, residence, level of education, seizure frequency, number of AEDs used, or seizure type, while a statistically significant relation between cognitive function among PWE and all of Orexin level (significantly lower in poor cognitive function), and total PSQI score (significantly higher in poor cognitive function), duration of illness (significantly higher in poor cognitive function), family history of neurological disease and sex. Male sex and positive family history significantly associated with poor cognition.

Table (4) demonstrated the best cutoff of orexin in prediction of poor cognition among PWE is ≤195 with area under curve 0.949, sensitivity 85.7%, specificity 91.7%, positive predictive value 94.4%, negative predictive value 79.7% and overall accuracy 88% ($p<0.001$). Table (5) demonstrated the relation between different factors (epilepsy duration, PSQI, serum orexin level, age, BMI, drug therapy and seizure frequency) and different domains of cognition assessed by MOCA. There is statistically significant negative correlation between orexin level, frequency of seizures, and epilepsy duration, PSQI and age, while a statistically significant positive correlation between orexin level and MOCA score exists as shown in table (6).

Table (1): Comparison between the studied groups regarding baseline data:

	Patient group (n=158)	**Control group (n=158)**	**p**
Age [mean ± SD]	32.2 ± 8.26	32.86 ± 7.36	0.451¥
Sex Male Female	 91 (57.6%) 67 (42.4%)	 98 (62%) 60 (38%)	 0.422§
BMI [mean ± SD]	26.63 ± 3.79	26.31 ± 3.76	0.456¥
PSQI [median (IQR)]	9(5 – 15)	4(3 – 6)	**<0.001****
Level of education <6 years 6 – 12 years >12 years	 27 (17.1%) 51 (32.3%) 80 (50.6%)	 31 (19.6%) 61 (38.6%) 66 (41.8%)	 0.18§§
Duration of illness [median (IQR)]	14 (9 – 22.25)		
Seizure frequency/month [Median (IQR)]	3(1 – 5)		
Number of antiepileptic drugs			

	Patient group (n=158)	Control group (n=158)	p
Monotherapy Polytherapy	56 (35.4%) 102 (64.6%)		
Seizures type Focal Focal with 2ry generalization GTC	 16 (10.1%) 15 (9.5%) 127 (80.4%)		
Residence Rural Urban	 81 (51.3%) 77 (48.7%)	 78 (49.4%) 80 (50.6%)	0.736§
Smoking Non-smoker Smoker	 124 (78.5%) 34 (21.5%)	 116 (73.4%) 42 (26.6%)	0.292§
Family history of neurological disease	44 (27.8%)	43 (27.2%)	0.9§
Orexin	125(31.2 – 500)	331.2(122.45 – 531.5)	<0.001**∞

§Chi square test §§Chi square for trend test ¥independent sample t test ∞Mann Whitney test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant BMI body mass index PSQI Pittsburgh Sleep Quality Index

Table (2): Comparison between groups regarding domains of MOCA scores:

	Patient group (n=158) Mean ± SD	Control group (n=158) Mean ± SD	P¥
Visuospatial	3.23 ± 0.89	4.35 ± 0.48	<0.001**
Naming	2.58 ± 0.69	2.99 ± 0.08	<0.001**
Attention	3.92 ± 1.14	5.18 ± 0.66	<0.001**
Language	2.38 ± 0.91	2.99 ± 0.08	<0.001**
Abstraction	1.62 ±0.49	2.0 ± 0	<0.001**
Recall	3.09 ± 1.18	4.5 ±0.5	<0.001**
Orientation	5.27 ± 1.28	5.99 ± 0.16	<0.001**
Total MoCA	22.16 ± 5.31	28.01 ± 1.18	<0.001**
Normal cognition **Mild cognition** **Moderate cognition**	60 (38%) 47 (29.7%) 51 (32.3%)	133 (84.2%) 25 (15.8%) 0 (0%)	<0.001**§§

§§Chi square for trend test ¥independent sample t test **p≤0.001 is statistically highly significant MOCA Montreal Cognitive Assessment

Table (3): relation between cognitive impairment among PWE and studied parameters:

	Normal cognition (n=60)	Abnormal cognition (n=98)	p
Age [mean ± SD]	32.63 ± 8.21	32.54 ± 8.32	0.505¥
Sex Male Female	 22 (24.2%) 38 (56.7%)	 69 (75.8%) 29 (43.3%)	<0.001**§
BMI [mean ± SD]	26.28 ± 4.27	26.84 ± 3.47	0.375¥
Level of education illiterate/read and write Basic High	 6 (10%) 15 (25%) 39 (65%)	 21 (21.4%) 36 (36.7%) 41 (41.8%)	0.005*§§
Residence Rural Urban	 31 (38.3%) 29 (37.7%)	 50 (61.7%) 48 (62.3%)	0.937§
Smoking			

	Normal cognition (n=60)	Abnormal cognition (n=98)	p
Non-smoker Smoker	58 (96.7%) 2 (3.3%)	65 (66.3%) 33 (33.7%)	<0.001**
Family history of neurological disease	11 (18.3%)	33 (33.7%)	0.037*
Duration of illness [median (IQR)]	9.5 (6.5 – 20)	17.5(12 – 23)	<0.001**$^{\infty}$
Seizure frequency/month [Median (IQR)]	2(0.5 – 4)	3(1 – 6.5)	0.008*$^{\infty}$
Number of antiepileptic drugs Monotherapy Polytherapy	 20 (35.7%) 40 (49.2%)	 36 (74.3%) 62 (50.8%)	0.664§
Seizures type Focal Focal with 2ry generalization GTC	 9 (56.3%) 8 (53.3%) 43 (33.9%)	 7 (43.7%) 7 (46.7%) 84 (66.1%)	0.096§
Orexin [median (IQR)]	500(250 – 500)	47.25(15.6 – 125)	<0.001**$^{\infty}$

§Chi square test §§Chi square for trend test $^{¥}$independent sample t test $^{\infty}$Mann Whitney test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant BMI body mass index

Table (4): Performance of Orexin in prediction of poor cognition among PWE:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≤195	0.949	85.7%	91.7%	94.4%	79.7%	88%	<0.001**

**p≤0.001 is statistically highly significant AUC area under curve PPV positive predictive value NPV negative predictive valu

Table (5): Correlation between domain of MOCA and studied parameters

	Epilepsy duration		Seizure frequency		BMI		PSQI		OREXIN		Age		Drugs	
	R	p	r	p	r	p	r	p	r	p	r	p	r	p
Visuospatial	-0.24	0.002*	-0.214	0.007*	-0.071	0.373	-0.365	<0.001**	0.69	<0.001**	-0.106	0.187	0.008	0.916
Naming	-0.186	0.02*	-0.148	0.063	-0.052	0.52	-0.078	0.165	0.746	<0.001**	-0.138	0.053	0.146	0.067
Attention	-0.245	0.002*	-0.232	0.003*	-0.112	0.161	-0.29	<0.001**	0.837	<0.001**	-0.083	0.293	0.052	0.518
Language	-0.201	0.011*	0.14	0.079	-0.031	0.703	-0.153	0.006*	0.812	<0.001**	-0.102	0.201	0.182	0.022*
Abstraction	-0.24	0.002*	-0.201	0.012*	-0.072	0.366	-0.186	<0.001**	0.825	<0.001**	-0.151	0.058	0.156	0.049*
Recall	-0.277	<0.001**	-0.22	0.006*	-0.089	0.264	-0.28	<0.001**	0.841	<0.001**	-0.104	0.196	0.136	0.089
Orientation	-0.148	0.068	-0.18	0.024	-0.038	0.632	-0.113	0.046*	0.796	<0.001**	-0.116	0.146	0.163	0.041*

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant BMI body mass index

Table (6): correlation between orexin level and studied parameters

	Epilepsy duration		Frequency		BMI		MOCA		PSQI		Age	
	R	p	r	P	r	p	r	p	r	p	r	p
orexin	-0.82	<0.001**	-0.247	0.002*	-0.003	0.974	0.924	<0.001**	-0.83	<0.001**	-0.291	<0.001**

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant BMI body mass index MOCA Montreal Cognitive Assessment PSQI Pittsburgh Sleep Quality Index

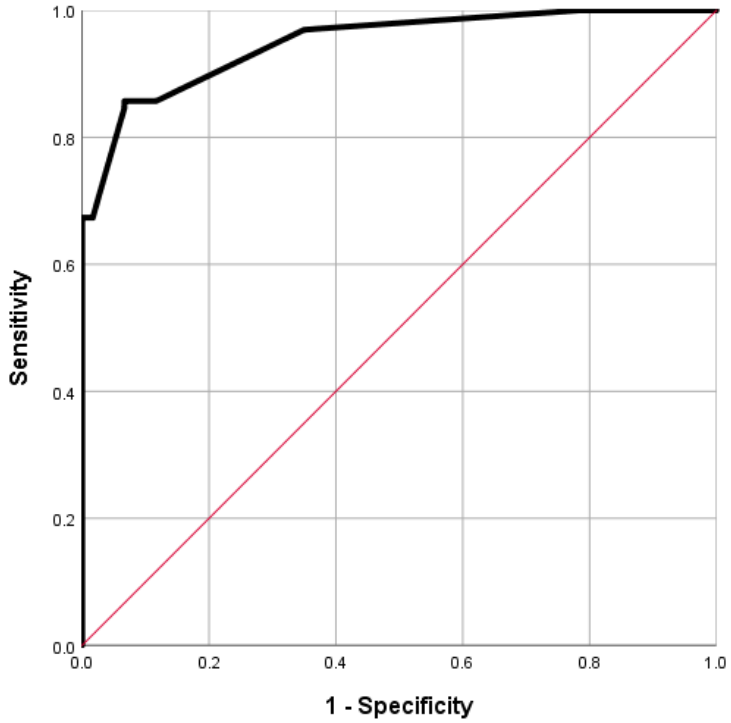


Figure (1): ROC curve showing performance of serum orexin in prediction of poor cognition among PWE

DISCUSSION

Epilepsy has many comorbidities such as cognitive impairment and sleep disorders, increasing burden on health care system. These comorbidities may affect patient quality of life and patient performance more than epilepsy itself. There is a growing attention to find novel biomarkers to early detect those comorbidities as early screening of cognitive impairment and sleep disorders optimize quality of life. The occurrence of repeated seizures together with status epilepticus cause oxidative stress and neuronal loss in brain areas responsible for cognitive processing, predominantly in hippocampus or entorhinal cortex **[4].**

The excitatory neuropeptide, Orexin-A is mainly secreted by hypothalamus and had been linked to many nervous system diseases, such as ischemic stroke, Alzheimer's disease, sleep disorder, and neurodegenerative diseases

In our study, serum Orexin A levels were significantly lower in PWE compared with age and sex matched controls. This is in accordance with **Li et al [26]** who used Orexin A as diagnostic marker of epilepsy and another previous study by **Arslan et al [27]** reported that reduced levels of serum orexin in epileptic patients, in addition the level of post-seizure orexin increased compared to the basal values, especially in seizures during sleep. **Cikriklar et al [28]** used orexin A to differentiate true epileptic from psychogenic seizures. As Orexin A manages subsequent ability of aberrant epileptiform activity to organize into seizures.

Our findings reported that 62% PWE suffer from different degrees of cognitive impairment assessed by MOCA finding was obtained. Similar findings were obtained by **Li et al [26]** as they stated that 67.53% of PWE has CI. Former studies showed variation in prevalence of CI in epilepsy,

as **Lodhi and Agarwal [29]** reported prevalence of 70-80% and **Wan et al [30]** stated that 72 % of PWE had CI.

All these data reflect the great impact of epilepsy on the cognitive function which is related to many factors including complex interactions among the etiologies of the epilepsy, the seizures themselves, interictal discharges, and antiepileptic drugs **[31].**

Patients with epilepsy with abnormal cognition has significant lower orexin A serum level than patients with normal cognition in accordance with **Li et al [26]** who reported that Orexin A is positively correlated with MOCA and Orexin A can be used for early detection as a warning index of cognitive dysfunction in epilepsy.

Orexin can affect the cognition and memory function through indirect effects as it regulates a wide variety of bodily functions that are known to impact the cognitive function. This process affects things like sleep, food, energy, and mood, which can all affect how well our brains work **[32]**. It also helps with important brain functions like paying attention, making decisions, and remembering things by keeping certain brain cells active **[33].**

There is a bidirectional interrelationship between epilepsy and sleep. Sleep disorders was reported in our patients more than our controls as assessed by PSQS. There is statistically significant negative correlation between PSQI, all domains of MOCA score except naming domain. Poor sleep is one of the risk factors of cognitive dysfunction as the prevalence of sleep disorders in epileptic patients with CI is more than those with normal cognition **[34].**

Our study showed that different epilepsy related characters are significantly associated with CI in PWE as male sex, smoking, family history of neurological diseases, duration of illness and frequency of seizures.

In our study, Male sex is associated with poor cognition; this is in accordance with **Zhong et al [35].** The effect of smoking on epilepsy is an important question; our findings suggested that smoking independently increased the risk of poor cognition in PWE which is in accordance with **Zhong et al [35].** Nicotine as excitatory transmitter increases release of glutamate, smoking is responsible for poor sleep quality increase risk of seizure and poor cognition **[36, 37].** Positive family history of epilepsy is associated with poor cognition; this is in accordance with **Lin et al [38].**

In our study, there is statistically significant negative correlation between epilepsy duration and all domains of MOCA score except orientation domain

Like our findings, **Seidenberg et al [39]** stated that the duration of epilepsy is related to cognitive impairment after 3 to 4 years of onset in PWE. In contrast **Taylor et al [40]** reported that even People with newly diagnosed epilepsy have CI even before starting medications most affected are memory and psycho-motor speed. **Witt et al [41]** reported that there was nearly 75% of newly diagnosed, untreated PWE having deficits in attention, executive functions, and memory

Our study stated that level of education is negatively correlated with CI; this is in accordance with other previous studies **[30, 40, 42].**

This finding may be due to patients with higher education having better understanding the nature of disease with better compliance to treatment and control of seizures also they have intellectual reserve and perform better in cognitive scales. Epileptic patients have lower educational opportunities in some families.

Wan et al [30] stated that preexisting intelligence or higher cognitive reserve are compensatory mechanisms delaying progression of CI, and this preexisting intelligence decreases rate of cognitive decline.

In our study, Seizure frequency is associated with affection in all cognitive domains except naming, language and orientation.

Seizure is the result of hyper-synchronized discharge causing electricity failure and neuronal hypoxia. Irreversible neuronal damage and frequent seizures increase time of abnormal discharge in the grey matter causing cognitive disability **[42]** also recurrent seizures affect brain plasticity **[2, 42].**

Vaessen et al [43] reported that abnormal gray and white matter is associated with cognitive decline in chronic epilepsy. Seizure control for one year is a protective factor for improving cognitive function **[42]**. However, people who had seizures more often had a higher risk of memory problems, but not problems in other thinking skills, compared to those who had fewer seizures. This shows that adults with epilepsy did not do well in many thinking skills, but having more seizures did not have a significant effect on thinking skills other than memory **[44]**.

There is a statistically significant positive correlation between number of AEDs and orientation, language and abstraction domains. Previous studies support our results **[2, 45, 46]**.

Martin et al [47] reported that PWE on polytherapy performed worse in all cognitive domains than patients on monotherapy. This is the effect of pharmacodynamics and pharmacokinetics that occur with time so balance

should be made between seizure control and drug adverse effects **[46]**.

We noted a significant negative correlation between serum orexin level and sleep quality assessed by PSQI.

Recently dual orexin receptor antagonists are for treating sleep impairment and insomnia in PWE **[48].** The ability of orexin to regulate sleep-wake states and promote arousal is mediated through the widely distributed orexin receptors hypothalamus, basal forebrain, tuberomammillary nucleus (TMN), periaqueductal gray, dorsal raphe (DR), and locus coeruleus **[49].**

Our results represent the first study to evaluate the best cutoff of orexin in prediction of poor cognition among PWE which was ≤195pg /ml with area under curve 0.949, sensitivity 85.7%, and specificity 91.7%.

CONCLUSIONS

prevention of cognitive impairment in epileptics is vital to reduce the disease burden on both individuals and the society; this can be done through improving the modifiable risk factors such as improving the educational level smoking prevention and proper seizure control. Serum orexin level below 195ng/ml could be used as a predictor for presence of cognitive impairment in PWE.

Disclosure of potential conflict of interest

The authors declare that they have no conflict of interest, and the study was not supported by any source of finding.

Ethics approval and constant to participate

The study was approved from the Institutional Ethics of the faculty of medicine. Zagazig University ZU-IRB #113661/10-12-2023). Written informed consent was obtained from all the participants after explaining the details and benefits as well as risks to them.

Availability of data

Data supporting the results of this article are included within article

REFERENCES

1.He M, Kolesar TA, Goertzen AL, Ng MC, Ko JH. Do Epilepsy Patients with Cognitive Impairment Have Alzheimer's Disease-like Brain Metabolism? Biomedicines. 2023; 11(4):1108.

2. Novak A, Vizjak K, Rakusa M. Cognitive Impairment in People with Epilepsy. J Clin Med. 2022 Jan 5;11(1):267. doi: 10.3390/jcm11010267. PMID: 35012007; PMCID: PMC8746065.

3.Xia J, Wang H, Zhang Q, Han Z. Modulation of P2X Purinoceptor 3 (P2X3) in Pentylenetetrazole-Induced Kindling Epilepsy in Rats. Med Sci Monit. 2018 Sep 5; 24:6165-6177. doi: 10.12659/MSM.910352. PMID: 30181529; PMCID: PMC6134887.

4.Holmes GL. Cognitive impairment in epilepsy: the role of network abnormalities. Epileptic Disord. 2015 Jun;17(2):101-16. doi: 10.1684/epd.2015.0739. PMID: 25905906; PMCID: PMC5410366.

5. Kataria L, Vaughn BV. Sleep and Epilepsy. Sleep Med Clin. 2016 Mar;11(1):25-38. doi: 10.1016/j.jsmc.2015.10.008. Epub 2016 Jan 9. PMID: 26972031.

6. Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun. 2018 Jan 8;9(1):88. doi: 10.1038/s41467-017-02577-y. PMID: 29311566; PMCID: PMC5758806.

7.Sudbrack-Oliveira P, Lima Najar L, Foldvary-Schaefer N, da Mota Gomes M. Sleep architecture in adults with epilepsy: a systematic review. Sleep Med. 2019 Jan;53:22-27. doi: 10.1016/j.sleep.2018.09.004. Epub 2018 Sep 21. PMID: 30388678.

8. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82. doi: 10.1111/epi.12550. Epub 2014 Apr 14. PMID: 24730690.

9.Barinaga M. New appetite-boosting peptides found. Science. 1998 Feb 20;279(5354):1134. doi: 10.1126/science.279.5354.1134. PMID: 9508686.

10.Sakurai T. Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy homeostasis. Sleep Med Rev. 2005 Aug;9(4):231-41. doi: 10.1016/j.smrv.2004.07.007. PMID: 15961331..

11.Harada S, Fujita-Hamabe W, Tokuyama S. Effect of orexin-A on post-ischemic glucose intolerance and neuronal damage. J Pharmacol Sci. 2011;115(2):155-63. doi: 10.1254/jphs.10264fp. Epub 2011 Jan 18. PMID: 21258173.

12.Xiong X, White RE, Xu L, Yang L, Sun X, Zou B, et al. Mitigation of murine focal cerebral ischemia by the hypocretin/orexin system is associated with reduced inflammation. Stroke. 2013 Mar;44(3):764-70. doi: 10.1161/STROKEAHA.112.681700. Epub 2013 Jan 24. PMID: 23349191; PMCID: PMC3638929.

13.Nixon JP, Mavanji V, Butterick TA, Billington CJ, Kotz CM, Teske JA. Sleep disorders, obesity, and aging: the role of orexin. Ageing Res Rev. 2015 Mar; 20:63-73. doi: 10.1016/j.arr.2014.11.001. Epub 2014 Nov 22. PMID: 25462194; PMCID: PMC4467809.

14.Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci. 1998 Dec 1;18(23):9996-10015. doi: 10.1523/JNEUROSCI.18-23-09996.1998. PMID: 9822755; PMCID: PMC6793310.
15.Roundtree HM, Simeone TA, Johnson C, Matthews SA, Samson KK, Simeone KA. Orexin Receptor Antagonism Improves Sleep and Reduces Seizures in Kcna1-null Mice. Sleep. 2016 Feb 1;39(2):357-68. doi: 10.5665/sleep.5444. PMID: 26446112; PMCID: PMC4712395.
16.Ida T, Nakahara K, Katayama T, Murakami N, Nakazato M. Effect of lateral cerebroventricular injection of the appetite-stimulating neuropeptide, orexin and neuropeptide Y, on the various behavioral activities of rats. Brain Res. 1999 Mar 13;821(2):526-9. doi: 10.1016/s0006-8993(99)01131-2. PMID: 10064841.
17.Ng MC. Orexin and Epilepsy: Potential Role of REM Sleep. Sleep. 2017 Mar 1;40(3). doi: 10.1093/sleep/zsw061. PMID: 28364414.
18.Uddin MS, Tewari D, Mamun AA, Kabir MT, Niaz K, Wahed MII, et al. Circadian and sleep dysfunction in Alzheimer's disease. Ageing Res Rev. 2020 Jul; 60:101046. doi: 10.1016/j.arr.2020.101046. Epub 2020 Apr 16. PMID: 32171783.
19. Havekes R, Heckman PRA, Wams EJ, Stasiukonyte N, Meerlo P, Eisel ULM. Alzheimer's disease pathogenesis: The role of disturbed sleep in attenuated brain plasticity and neurodegenerative processes. Cell Signal. 2019 Dec; 64:109420. doi: 10.1016/j.cellsig.2019.109420. Epub 2019 Sep 16. PMID: 31536750.
20.Li Y, Shao L, Mou Y, Zhang Y, Ping Y. Sleep, circadian rhythm and gut microbiota: alterations in Alzheimer's disease and their potential links in the pathogenesis. Gut Microbes. 2021 Jan-Dec;13(1):1957407. doi: 10.1080/19490976.2021.1957407. PMID: 34520319; PMCID: PMC8463034.
21.Wu H, Dunnett S, Ho YS, Chang RC. The role of sleep deprivation and circadian rhythm disruption as risk factors of Alzheimer's disease. Front Neuroendocrinol. 2019 Jul; 54:100764. doi: 10.1016/j.yfrne.2019.100764. Epub 2019 May 15. PMID: 31102663.
22.Villano I, Messina A, Valenzano A, Moscatelli F, Esposito T, Monda V, et al. Basal Forebrain Cholinergic System and Orexin Neurons: Effects on Attention. Front Behav Neurosci. 2017 Jan 31; 11:10. doi: 10.3389/fnbeh.2017.00010. PMID: 28197081; PMCID: PMC5281635.
23.Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4. PMID: 2748771.
24.Suleiman KH, Yates BC, Berger AM, Pozehl B, Meza J. Translating the Pittsburgh Sleep Quality Index into Arabic. West J Nurs Res. 2010 Mar;32(2):250-68. doi: 10.1177/0193945909348230. Epub 2009 Nov 14. PMID: 19915205.
25.Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221. x. Erratum in: J Am Geriatr Soc. 2019 Sep;67(9):1991. PMID: 15817019.
26.Li J, Wang Q, Qian J, Chen X, Li D, Song C. Correlation of serum Orexin-A level with cognitive function and serum inflammatory cytokines in epileptic patients. Am J Transl Res. 2023 Jun 15;15(6):4110-4117. PMID: 37434836; PMCID: PMC10331673.
27.Arslan GA, Saygi S, Bodur E, Cicek C, Tezer FI. Relation between orexin A and epileptic seizures. Epilepsy Res. 2022 Aug; 184:106972. doi: 10.1016/j.eplepsyres.2022.106972. Epub 2022 Jun 26. PMID: 35772324.
28.Çikriklar HI, Kotan D, Yücel M, Ceylan M, Çiftçi GG, Bayraktutan ÖF, et al. The role of Orexin-A levels in epileptic seizure. Neurosci Lett. 2020 Aug 24; 734:135097. doi: 10.1016/j.neulet.2020.135097. Epub 2020 May 30. PMID: 32485288.
29.Lodhi S and Agrawal N. Neurocognitive problems in epilepsy. Advances in Psychiatric Treatment. 2012;18(3):232-240. doi:10.1192/apt.bp.110.007930.
30.Wan H, Liu Q, Chen C, Dong W, Wang S, Shi W, et al. An Integrative Nomogram for Identifying Cognitive Impairment Using Seizure Type and Cerebral Small Vessel Disease Neuroimaging Markers in Patients with Late-Onset Epilepsy of Unknown Origin. Neurol Ther. 2024 Feb;13(1):107-125. doi: 10.1007/s40120-023-00566-6. Epub 2023 Nov 29. PMID: 38019380; PMCID: PMC10787714.
31.Helmstaedter C, Aldenkamp AP, Baker GA, Mazarati A, Ryvlin P, Sankar R. Disentangling the relationship between epilepsy and its behavioral comorbidities - the need for prospective studies in new-onset epilepsies. Epilepsy Behav. 2014 Feb; 31:43-7. doi:

10.1016/j.yebeh.2013.11.010. Epub 2013 Dec 13. PMID: 24333577.
32.Toor B, Ray LB, Pozzobon A, Fogel SM. Sleep, Orexin and Cognition. Front Neurol Neurosci. 2021; 45:38-51. doi: 10.1159/000514960. Epub 2021 May 28. PMID: 34052810.
33.Chen Q, de Lecea L, Hu Z, Gao D. The hypocretin/orexin system: an increasingly important role in neuropsychiatry. Med Res Rev. 2015 Jan;35(1):152-97. doi: 10.1002/med.21326. Epub 2014 Jul 12. PMID: 25044006.
34. Oyegbile-Chidi T, Harvey D, Eisner J, Dunn D, Jones J, Byars A, et al. The Relationship Between Sleep, Cognition and Behavior in Children with Newly-Diagnosed Epilepsy Over 36 Months. Front Neurol. 2022 Jul 26; 13:903137. doi: 10.3389/fneur.2022.903137. PMID: 35959398; PMCID: PMC9360804.
35.Zhong R, Lu Y, Chen Q, Li M, Zhao Q, Zhang X, et al. Sex differences in factors associated with quality of life in patients with epilepsy in Northeast China. Epilepsy Behav. 2021 Aug;121(Pt A):108076. doi: 10.1016/j.yebeh.2021.108076. Epub 2021 May 31. PMID: 34082318.
36.Dugas EN, Sylvestre MP, O'Loughlin EK, Brunet J, Kakinami L, Constantin E, et al. Nicotine dependence and sleep quality in young adults. Addict Behav. 2017 Feb; 65:154-160. doi: 10.1016/j.addbeh.2016.10.020. Epub 2016 Oct 25. PMID: 27816041.
37.Bazil CW. Seizure modulation by sleep and sleep state. Brain Res. 2019 Jan 15; 1703:13-17. doi: 10.1016/j.brainres.2018.05.003. Epub 2018 May 18. PMID: 29782849.
38.Lin F, Han J, Xue T, Lin J, Chen S, Zhu C, et al. Predicting cognitive impairment in outpatients with epilepsy using machine learning techniques. Sci Rep. 2021 Oct 8;11(1):20002. doi: 10.1038/s41598-021-99506-3. PMID: 34625614; PMCID: PMC8501137.
39.Seidenberg M, Pulsipher DT, Hermann B. Cognitive progression in epilepsy. Neuropsychol Rev. 2007 Dec;17(4):445-54. doi: 10.1007/s11065-007-9042-x. Epub 2007 Nov 8. PMID: 17990122.
40.Taylor J, Kolamunnage-Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA; SANAD study group. Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? Epilepsia. 2010 Jan;51(1):48-56. doi: 10.1111/j.1528-1167.2009.02195. x. Epub 2009 Jul 2. PMID: 19583779.
41.Witt JA, Helmstaedter C. Should cognition be screened in new-onset epilepsies? A study in 247 untreated patients. J Neurol. 2012 Aug;259(8):1727-31. doi: 10.1007/s00415-012-6526-2. Epub 2012 May 12. PMID: 22580844.
42.Wang L, Chen S, Liu C, Lin W, Huang H. Factors for cognitive impairment in adult epileptic patients. Brain Behav. 2020 Jan;10(1): e01475. doi: 10.1002/brb3.1475. Epub 2019 Dec 21. PMID: 31863643; PMCID: PMC6955925.
43.Vaessen MJ, Jansen JF, Vlooswijk MC, Hofman PA, Majoie HJ, Aldenkamp AP, et al. White matter network abnormalities are associated with cognitive decline in chronic epilepsy. Cereb Cortex. 2012 Sep;22(9):2139-47. doi: 10.1093/cercor/bhr298. Epub 2011 Oct 29. PMID: 22038907.
44.Arinzechi EO, Ogunrin OA, Nwosu CM, Nwani PO, Enwereji KO, Asomugha LA, et al. Seizure frequency and risk of cognitive impairment in people living with epilepsy in a sub-urban community in South Eastern Nigeria. J Clin Neurosci. 2019 Jan; 59:98-105. doi: 10.1016/j.jocn.2018.10.120. Epub 2018 Nov 13. PMID: 30446372.
45.Miller LA, Galioto R, Tremont G, Davis J, Bryant K, Roth J, et al. Cognitive impairment in older adults with epilepsy: Characterization and risk factor analysis. Epilepsy Behav. 2016 Mar; 56:113-7. doi: 10.1016/j.yebeh.2016.01.011. Epub 2016 Feb 7. PMID: 26859320.
46.Piazzini A, Canevini MP, Turner K, Chifari R, Canger R. Elderly people and epilepsy: cognitive function. Epilepsia. 2006;47 Suppl 5:82-4. doi: 10.1111/j.1528-1167.2006.00884. x. PMID: 17239113.
47.Martin RC, Griffith HR, Faught E, Gilliam F, Mackey M, Vogtle L. Cognitive functioning in community dwelling older adults with chronic partial epilepsy. Epilepsia. 2005 Feb;46(2):298-303. doi: 10.1111/j.0013-9580.2005.02104. x. PMID: 15679511.
48.Berteotti C, Calvello C, Liguori C. Role of the orexin system in the bidirectional relation between sleep and epilepsy: New chances for patients with epilepsy by the antagonism to orexin receptors? Epilepsia. 2023 Aug;64(8):1991-2005. doi: 10.1111/epi.17661. Epub 2023 Jun 9. PMID: 37212716.
49.Xie X, Crowder TL, Yamanaka A, Morairty SR, Lewinter RD, Sakurai T, et al: GABA(B) receptor-mediated modulation of hypocretin/orexin neurones in mouse hypothalamus. J Physiol 2006; 574:399–414.

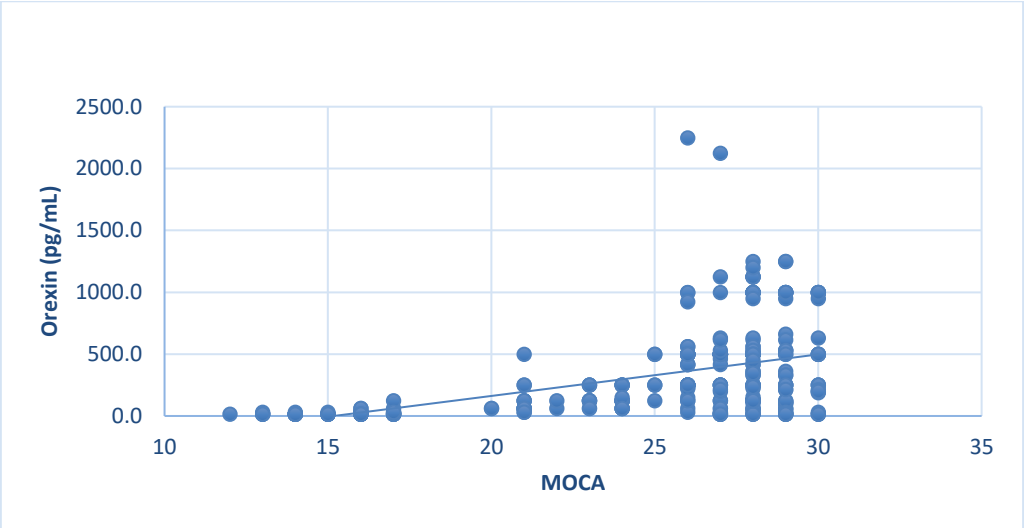


Figure (S1): Scatter dot plot showing significant positive correlation between Orexin and MOCA (r=0.924, p<0.001)

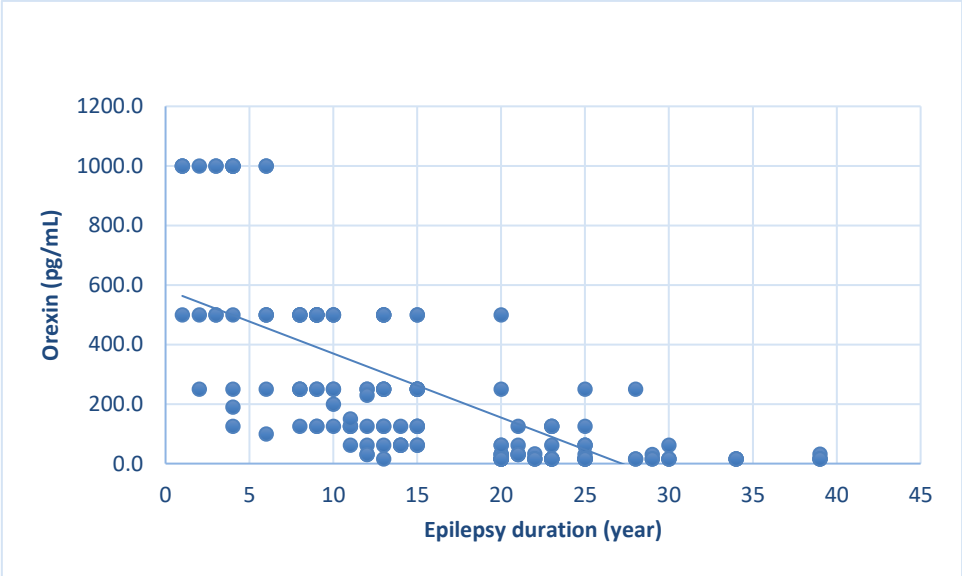
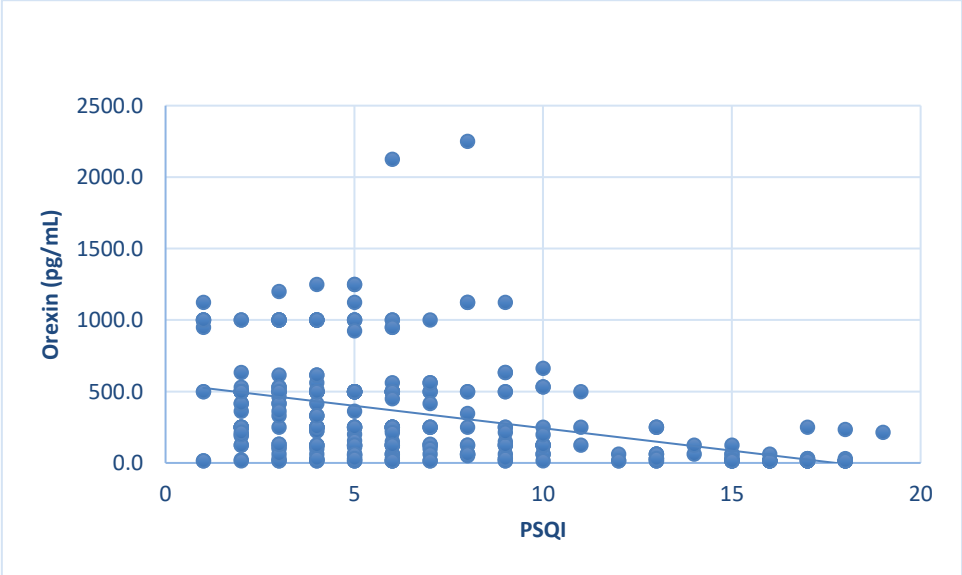


Figure (S2): Scatter dot plot showing significant negative correlation between Orexin and epilepsy duration (r=-0.82, p<0.001)



Citation

helal, R., AbdAllah, A., Fathy, S., Hashim, N. Serum Orexin in Epilepsy: Relation to Cognitive Impairment and Sleep Disorders. *Zagazig University Medical Journal*, 2025; (): -. doi: 10.21608/zumj.2024.279212.3278