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Original Article

Correlation of serum Orexin-A level with cognitive function and serum inflammatory cytokines in epileptic patients

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Abstract: Objective: This study was designed to analyze the associations of serum Orexin-A level with cognitive function and serum inflammatory cytokines in epileptic patients. Methods: Totally 77 epileptic patients treated in Suqian First Hospital between January 2019 and January 2022 were retrospectively analyzed as the observation group, and 65 healthy individuals who had a physical examination in Suqian First Hospital during the same period were enrolled as the control group. The Mini-Mental State Examination (MMSE) was conducted in participants in the two groups, and the enzyme-linked immunosorbent assay (ELISA) was conducted for quantifying serum Orexin-A, interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Additionally, the Pearson correlation test was used for analyzing the associations of Orexin-A with MMSE, IL-1β, IL-6, and TNF-α in the patients, and receiver operating characteristic (ROC) curves were drawn for determining the diagnostic value of Orexin-A in epilepsy and cognitive dysfunction in epileptic patients. The independent risk factors for cognitive impairment in epileptic patients were analyzed by multivariate logistic regression analysis. Results: Epileptic patients showed a significantly lower serum Orexin-A level than the control group ($P < 0.05$), and the area under the curve (AUC) of Orexin-A in epilepsy diagnosis was 0.879. Additionally, epileptic patients had notably lower MMSE scores than the control group ($P < 0.05$). The Pearson correlation test revealed a positive association of Orexin-A with MMSE score and negative correlations of Orexin-A with IL-1β, IL-6, and TNF-α levels ($P < 0.05$). The AUC of Orexin-A in diagnosing cognitive dysfunction in epileptic patients was 0.908. According to multivariate analysis, lower education level, more severe EEG abnormalities and a lower Orexin-A level were independent risk factors for cognitive impairment in epileptic patients. Conclusion: Orexin-A can act as a diagnostic marker for epileptic patients, and its level is positively related with cognitive function of patients, but negatively related to the degree of inflammation. It is promising to be an early warning index for epilepsy and cognitive dysfunction in patients.

Keywords: Epilepsy, Orexin-A, cognitive function, inflammatory cytokines

Introduction

Epilepsy is a frequent problem that affects 65 million people worldwide, and there are 10 million epileptic patients in China [1, 2]. It is characterized by the excessive discharge of brain neurons leading to long-term spontaneous seizures due to the imbalance of excitatory and inhibitory activities in the neural network, accompanied by cognitive disorders such as language dysfunction, memory dysfunction, depression, anxiety and others that bring serious physical and psychological pains to patients [3, 4]. At present, although many drugs are available clinically to intervene and prevent the development of epilepsy, about 30% of epileptic patients cannot get control with common epilepsy drugs and finally develop into intractable epilepsy [5].

Research has revealed that the brain structure of epileptic patients is abnormal, and the hippocampus of patients with chronic epilepsy is smaller than that of healthy individuals [6]. Repeated abnormal discharge of neurons will change the connection between synapses of neurons, which will trigger the change or deletion of neurons in the hippocampus of the brain, and the loss or change of neurons will interrupt the continuity of synapses and affect learning

and memory [7]. Currently, epilepsy with cognitive dysfunction has aroused widespread concern. The cognitive impairment in epileptic patients can progress to epileptic dementia, which severely affects the society and families [8]. Therefore, it is of profound importance to evaluate the severity of cognitive dysfunction in epileptic patients as soon as possible.

Orexin-A is an excitatory neuropeptide, mainly secreted by hypothalamus and extensively distributed in blood and the whole central nervous system [9]. According to studies [10, 11], Orexin-A is correlated with many nervous system diseases, such as ischemic stroke, Alzheimer's disease, sleep disorder, and neurodegenerative diseases. Reportedly, Orexin-A can activate the neurons of aged rats and improve their cognitive ability and attention [12].

With the known role of Orexin-A in the nervous system as the theoretical basis, this study analyzed the association of serum Orexin-A level with cognitive function in epileptic patients to offer a theoretical basis for clinical exploration of new serum biomarkers.

Materials and methods

Patient information

A total of 77 epileptic patients admitted to Suqian First Hospital between January 2019 and January 2022 were enrolled into the observation group, and retrospectively analysed, including 41 men and 36 women with a mean age of (47.12±10.91) years old. Additionally, 65 healthy individuals who received physical examination in the hospital during the same time period were enrolled into the control group, including 22 females and 43 males with a mean age of (49.48±11.24) years old. This study was carried out with approval of the Medical Ethics Committee of Suqian First Hospital (ethical approval number: 20190421).

Inclusion and exclusion criteria of observation group

Inclusion criteria: Individuals who were diagnosed with epilepsy according to EEG, and met the diagnostic guidelines issued by the International Epilepsy Union in 2017 [13]; individuals who were able to correctly understand the contents of the scale and make corresponding answers; and individuals with complete clinical data.

Exclusion criteria: Patients comorbid with other degenerative brain diseases; patients who suffered congenital immunodeficiency, acute infectious diseases, or severe inflammation; or patients with other malignant tumors.

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 interleukin-6 (IL-6), Orexin-A, interleukin-1β (IL-1β), as well as tumor necrosis factor-α (TNF-α) were quantified by Enzyme-linked immunosorbent assay with kits from Elabscience Biotechnology Co., Ltd. (E-EL-H6156, E-EL-H1015c, E-EL-H0149c, as well as E-EL-H0109c) under strict guidelines.

Outcome measures

(1) The serum Orexin-A, IL-1β, IL-6 as well as TNF-α in the two groups were compared. (2) The cognitive ability of each participant was assessed by the Mini-Mental State Examination (MMSE), and the two groups' MMSE scores were compared [14]. The scale covers place orientation, time orientation, attention and calculation, immediate memory, language, delayed memory, as well as visual space. It has 30 questions totally, with 1 point for each right answer and 0 points for wrong one or choice of unknown. The total score of the scale is between 0-30 points, with a score of 27-30 as normal cognition, and a score of < 27 as cognitive impairment. (3) The Pearson correlation test was conducted for association analysis of Orexin-A level with MMSE score, IL-1β, IL-6 as well as TNF-α levels in epileptic patients. (4) The diagnostic value of Orexin-A for epilepsy and cognitive dysfunction in epileptic patients was evaluated using ROC curve. (5) Multivariate analysis was adopted for analysis of the independent risk factors of cognitive impairment in epileptic patients.

Statistical analyses

SPSS20.0 software was used for data analysis, and GraphPad Prism 7 was used for figure rendering. Counted data (%) were analyzed via the chi-square test, and presented as χ^2. Intergroup comparison of measured data (Mean ±

Table 1. Baseline data

	Observation group (n=77)	Control group (n=65)	T/χ^2 value	*P* value
Gender			2.430	0.119
Male	41 (53.25)	43 (66.15)		
Female	36 (46.75)	22 (33.85)		
Age (years)	47.12±10.91	49.48±11.24	1.267	0.207
Body mass index (kg/m^2)	23.12±2.48	22.85±2.89	0.599	0.550
Education level			0.336	0.845
< 6 years	13 (16.88)	13 (20.00)		
6-12 years	54 (70.13)	45 (69.23)		
> 12 years	10 (12.99)	7 (10.77)		
Place of residence			1.534	0.216
Urban area	56 (72.73)	53 (81.54)		
Rural area	21 (27.27)	12 (18.46)		
Age of onset				
< 18 years old	8 (10.39)			
≥ 18 years old	69 (89.61)			
Course of disease (years)	7.01±3.09			
Seizure type				
Local attack	39 (50.65)			
Comprehensive attack	23 (29.87)			
Unclassifiable attack	15 (19.48)			
Medication				
No	5 (6.49)			
One kind of drug	32 (41.56)			
Two kinds of drugs	30 (38.96)			
Three kinds of drugs	10 (12.99)			
Abnormal electroencephalogram				
Normal	5 (6.49)			
Mildly abnormal	17 (22.08)			
Moderately abnormal	43 (55.84)			
Seriously abnormal	12 (15.58)			

SD) was conducted by the independent-samples T test. The Pearson correlation test was conducted for analyzing the relationships of Orexin-A level with MMSE score, IL-6, IL-1β as well as TNF-α levels in epileptic patients, and ROC curves were drawn to analyze the diagnostic value of Orexin-A for epilepsy and cognitive dysfunction in epileptic patients. Multivariate logistic regression analysis was done for analysis of the independent risk factors of cognitive impairment in epileptic patients. P < 0.05 was a significant difference.

Results

Baseline data

According to comparison of baseline data, the two groups were comparable in gender, education level, age, BMI, or place of residence (P > 0.05, **Table 1**).

Diagnostic value of Orexin-A for epilepsy

Comparison of Orexin-A level between the observation and control groups revealed a significantly lower Orexin-A level in the observation group than that in the control group. According to ROC curve of Orexin-A for epilepsy diagnosis, the AUC was 0.879 (**Figure 1**).

Association of Orexin-A with cognitive ability of epileptic patients

According to inter-group comparison of MMSE scores, the observation group got notably lower MMSE scores than the control group (P < 0.05).

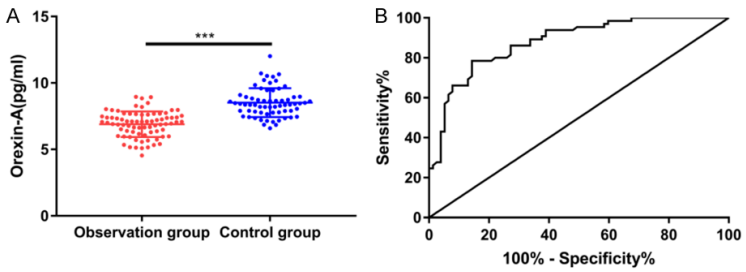

Figure 1. Diagnostic value of Orexin-A for epilepsy. A. The observation group showed a significantly lower Orexin-A level than the control group (P < 0.001). B. In the ROC curve of Orexin-A in diagnosing epilepsy, the AUC, cut-off value, sensitivity and specificity were 0.879, > 7.755, 78.46% and 85.71%, respectively.

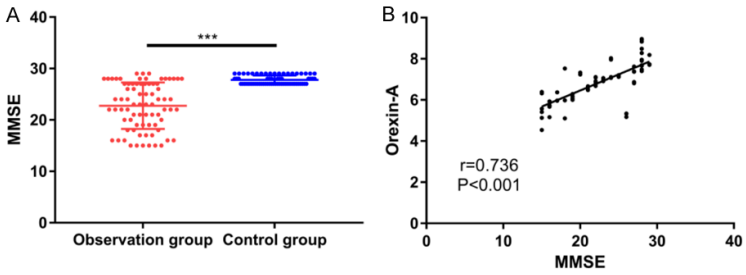

Figure 2. Association of Orexin-A with cognitive ability of epileptic patients. A. The observation group got significantly lower MMSE scores than the control group (P < 0.001). B. Orexin-A had a positive correlation with MMSE score (r=0.736, P < 0.001).

The Pearson correlation analysis revealed a positive association between Orexin-A with MMSE score (P < 0.001, **Figure 2**).

Expression of inflammatory cytokines in epileptic patients

Quantification of IL-6, IL-1β as well as TNF-α in the observation and control groups revealed notably higher levels of all 3 in the former group than those in the latter (P < 0.05, **Figure 3**).

Correlations of Orexin-A with inflammatory cytokines in epileptic patients

Pearson correlation analysis on the association of Orexin-A with inflammatory cytokines in epileptic patients revealed negative associations of Orexin-A with inflammatory cytokines (P < 0.001, **Figure 4**).

Diagnostic value of Orexin-A in cognitive dysfunction of epileptic patients

All epileptic patients were grouped based on MMSE score, in which those with MMSE score ≥ 27 points were assigned to the normal cognition group (NC group, n=25) and the others were assigned to the impaired cognition group (IC group, n= 52). The rate of cognitive dysfunction was 67.53%. According to comparison of Orexin-A level between the two groups, the IC group showed a notably lower Orexin-A level than the NC Group (P < 0.05), and the AUC of Orexin-A in diagnosing cognitive dysfunction of epileptic patients was 0.908 (**Figure 5**).

Univariate analysis of cognitive impairment in epileptic patients

By comparing the clinical data of the cognitive impairment group and normal cognitive function group, we found that there were significant differences in education level, course of disease, seizure type, medication, abnormal EEG, IL-6, Orexin-A, IL-1β as well as TNF-α between the two groups (P < 0.05, **Table 2**).

Multivariate analysis of cognitive impairment in epileptic cases

We conducted multivariate logistics regression analysis of the indicators with differences in univariate analysis and found that lower education level, more severe EEG abnormalities, and a lower Orexin-A level were independent risk factors for cognitive impairment in epileptic cases (**Table 3**).

Discussion

Epilepsy is a common chronic nervous system disease. Patients with epilepsy have seizures due to repeated abnormal discharges of neurons, and suffer many adverse consequences, such as trauma, disability, and abnormal behavior, among which cognitive dysfunction is one of the serious adverse consequences of epilepsy [15, 16]. In the present study, the MMSE was adopted for evaluating the cognitive level of epileptic patients. As a result, 67.53% of epileptic patients were found to suffer cognitive dysfunction, and the observation group had nota-

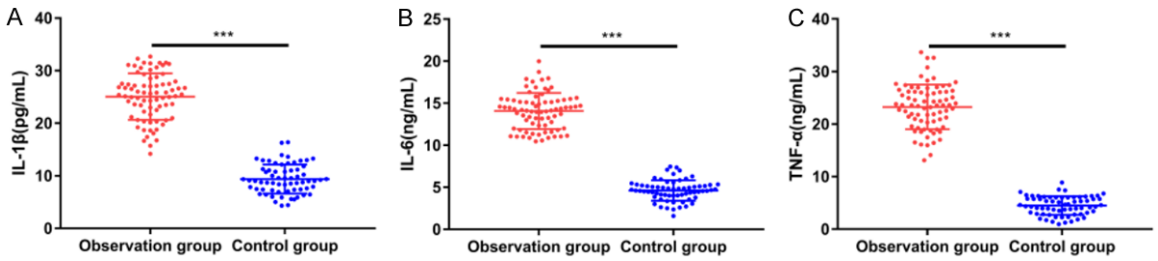

Figure 3. Expression of inflammatory cytokines in epileptic patients. A. The observation group showed a significantly higher IL-1β level than the control group (P < 0.001). B. The observation group showed a significantly higher IL-6 level than the control group (P < 0.001). C. The observation group showed a significantly higher TNF-α level than the control group (P < 0.001).

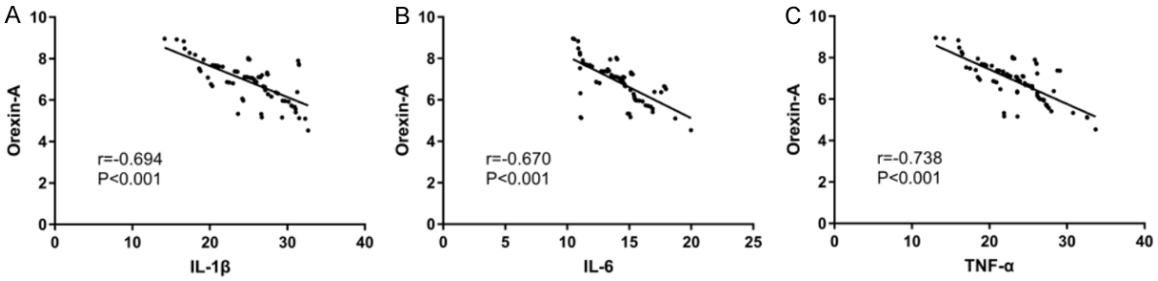

Figure 4. Associations of Orexin-A with inflammatory cytokines in epileptic patients. A. Orexin-A had a negative correlation with IL-1β (r=-0.694, P < 0.001). B. Orexin-A had a negative correlation with IL-6 (r=-0.670, P < 0.001). C. Orexin-A had a negative correlation with TNF-α (r=-0.738, P < 0.001).

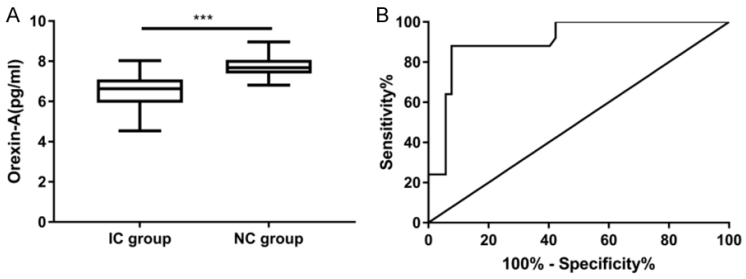

Figure 5. Diagnostic value of Orexin-A in cognitive dysfunction of epileptic patients. A. The IC group showed a significantly lower Orexin-A level than the NC group (P < 0.001). B. In the ROC curve of Orexin-A for diagnosing cognitive dysfunction of epilepsy, the AUC, cut-off value, sensitivity and specificity were 0.908, > 7.350, 88.00% and 92.31%, respectively.

bly lower MMSE scores than the control group, suggesting a notable incidence of cognitive dysfunction in epileptic patients. Wang et al. [17] conducted multivariate analysis on 257 epileptic patients, and found that seizure frequency, education level, types of antiepileptic drugs as well as depression greatly affected the cognition of epileptic patients, among which good seizure control, high education level, single drug therapy and healthy mental state were the protective factors for cognitive function. However, Karaaslan et al. [18] found that epileptic patients had significantly decreased cognitive dysfunction even though they had no frequent seizures and their epilepsy was not drug-resistant. Therefore, attention is required for cognitive impairment of epileptic patients.

The mechanism of epileptic seizure is complex. At the current stage, abnormal neurotransmitters, abnormal opening of ion channels, glial cells, immune response, inflammatory cytokines and genetic genes are considered as factors triggering epileptic seizures [19, 20]. According to research in recent years, Orexin-A is strongly linked to seizure of epilepsy. In the present study, the observation group presented a notably lower Orexin-A level than the control group, suggesting the possibility of using Orexin-A for epilepsy diagnosis. ROC curves were drawn for determining the diagnostic function of Orexin-A in epilepsy, and the AUC, sensitivity as well as

Table 2. Multivariate analysis

	IC group (n=52)	NC group (n=25)	T/χ^2 value	*P* value
Gender			1.719	0.190
Male	25 (48.08)	16 (64.00)		
Female	27 (51.92)	9 (36.00)		
Age (years)	47.75±10.52	45.80±11.80	0.732	0.467
Body mass index (kg/m^2)	23.21±2.61	22.94±2.22	0.445	0.657
Education level			7.496	0.024
< 6 years	9 (17.31)	4 (16.00)		
6-12 years	40 (76.92)	14 (56.00)		
> 12 years	3 (5.77)	7 (28.00)		
Place of residence			0.417	0.518
Cities and towns (56)	39 (75.00)	17 (68.00)		
Rural area (21)	13 (25.00)	8 (32.00)		
Age of onset			0.227	0.634
< 18 years old	6 (11.54)	2 (8.00)		
≥ 18 years old	46 (88.46)	23 (92.00)		
Course of disease (years)	7.71±2.96	5.56±2.89	3.007	0.004
Seizure type			9.265	0.010
Local attack	21 (40.38)	18 (72.00)		
Comprehensive attack	21 (40.38)	2 (8.00)		
Unclassifiable attack	10 (19.23)	5 (20.00)		
Medication			8.959	0.030
No	1 (1.92)	4 (16.00)		
One kind of drug	19 (36.54)	13 (52.00)		
Two kinds of drugs	24 (46.15)	6 (24.00)		
Three kinds of drugs	8 (15.38)	2 (8.00)		
Abnormal electroencephalogram			11.320	0.010
Normal	1 (1.92)	4 (16.00)		
Mildly abnormal	8 (15.38)	9 (36.00)		
Moderately abnormal	34 (65.38)	9 (36.00)		
Seriously abnormal	9 (17.31)	3 (12.00)		
Orexin-A (pg/ml)	6.48±0.82	7.75±0.59	6.920	< 0.001
IL-1β (pg/ml)	26.06±3.28	22.98±5.67	3.016	0.004
IL-6 (ng/ml)	14.55±2.04	13.08±2.07	2.947	0.004
TNF-α (ng/ml)	24.01±3.29	21.70±5.51	2.297	0.024

specificity were 0.879, 78.46% as well as 85.71%, respectively, which indicated a good diagnostic value of Orexin-A in epilepsy. In addition, Orexin-A was found to have a positive correlation with MMSE score of epileptic patients. The research by Samzadeh et al. [21] revealed that long-term seizures of epilepsy might trigger a decrease in the concentration of Orexin-A in cerebrospinal fluid, and a low Orexin-A level in cerebrospinal fluid was usually negatively linked to the duration of status epilepticus, with a lower Orexin-A level in patients with status epilepticus who had worse prognosis during the one-month observation period. The results suggest that Orexin-A may have diagnostic and prognostic use in epilepsy.

Inflammation is strongly related with epileptic seizure, and many pro-inflammatory cytokines are implicated in the progression of epilepsy [22]. According to animal experiments, the pro-inflammatory cytokines increase after seizure of epilepsy, which indicates that inflammatory cytokines might take a crucial part in the evaluation of epilepsy. However, it still lacks the specificity to judge the condition of epileptic

Table 3. Multivariate analysis

	B	S.E,	Wals	Sig.	Exp (B)	95% C.I. of EXP (B)	
						Lower limit	Upper limit
Education level	-2.045	0.995	4.221	0.040	0.129	0.018	0.910
Abnormal electroencephalogram	1.703	0.761	5.006	0.025	5.492	1.235	24.416
Orexin-A	-3.290	1.198	7.544	0.006	0.037	0.004	0.390

patients only by inflammatory cytokines [23, 24]. In the present study, the observation group showed significantly higher IL-6, IL-1β, and TNF-α levels than the control group, which indicated that inflammation was related to occurrence of epilepsy and participated in the pathogenesis of epilepsy. Then the correlations of Orexin-A with TNF-α, IL-6 as well as IL-1β were analyzed, and positive correlations were found between them. Finally, the epileptic patients were assigned to a normal cognition group or an impaired cognition group. Patients with cognitive dysfunction showed a significantly lower Orexin-A than the normal cognitive group. According to ROC curve, the AUC of Orexin-A for cognitive dysfunction diagnosis in epileptic patients was 0.908, and the sensitivity and specificity were 88.00% and 92.31%, respectively. This suggests that we can evaluate the severity of cognitive dysfunction by monitoring serum Orexin-A in epileptic patients, and the serum Orexin-A level can serve as one early warning index for epileptic patients with cognitive dysfunction. Finally, through multivariate analysis, we found that lower education level, more severe EEG abnormalities and a lower Orexin-A level were independent risk factors for cognitive impairment in epileptic patients, suggesting that we can prevent cognitive impairment in advance in epileptic patients by observing these risk factors. A study by Wang et al. [25] conducted a multivariate analysis of 257 adult epileptic patients. Their study also found that a lower education level was one risk factor for the cognitive function of patients with epilepsy. Moreover, their study also discovered that more anti-epileptic drugs were one risk factor for the cognitive function. The reason may be that patients had lighter epilepsy symptoms and therefore required fewer drugs. At the same time, more patients were treated with more than three kinds of antidepressants, suggesting that more attention should be paid to patients who use more than three drugs.

However, the study has some limitations. First, we have not analyzed the hospitalization and medication of epileptic patients, and the factors that affect the serum Orexin-A level are not excluded. Second, whether Orexin-A can serve as one judgment index of different curative effects remains unclear. Last, Orexin-A level has an association with cognitive function and inflammatory cytokines of epileptic patients, but the specific mechanism is still under investigation, and a lot of basic experiments are required.

To sum up, Orexin-A can act as a diagnostic marker for epileptic patients, and its level is correlated positively with cognitive function of patients, but negatively with the degree of inflammation. It is promising as an early warning index for epilepsy and cognitive dysfunction in patients.

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Disclosure of conflict of interest

None.

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