ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2023 October 19; 13(10): 714-815

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJP* as 3.1; IF without journal self cites: 2.9; 5-year IF: 4.2; Journal Citation Indicator: 0.52; Ranking: 91 among 155 journals in psychiatry; and Quartile category: Q3.

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NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

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https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
October 19, 2023

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World J Psychiatry 2023 October 19; 13(10): 714-723

DOI: 10.5498/wjp.v13.i10.714

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalogram slow wave/fast wave frequency ratio in epilepsy

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Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cicero N, Italy; Karakose T, Turkey

Received: August 16, 2023
Peer-review started: August 16, 2023
First decision: August 31, 2023
Revised: September 8, 2023
Accepted: September 22, 2023
Article in press: September 22, 2023
Published online: October 19, 2023

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Abstract

BACKGROUND

Cognitive dysfunction in epileptic patients is a high-incidence complication. Its mechanism is related to nervous system damage during seizures, but there is no effective diagnostic biomarker. Neuronal pentraxin 2 (NPTX2) is thought to play a vital role in neurotransmission and the maintenance of synaptic plasticity. This study explored how serum NPTX2 and electroencephalogram (EEG) slow wave/fast wave frequency ratio relate to cognitive dysfunction in patients with epilepsy.

AIM

To determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in epilepsy patients.

METHODS

The participants of this study, conducted from January 2020 to December 2021, comprised 74 epilepsy patients with normal cognitive function (normal group), 37 epilepsy patients with cognitive dysfunction [epilepsy patients with cognitive dysfunction (ECD) group] and 30 healthy people (control group). The mini-mental state examination (MMSE) scale was used to evaluate cognitive function. We determined serum NPTX2 levels using an enzyme-linked immunosorbent kit and calculated the signal value of EEG regions according to the EEG recording. Pearson correlation coefficient was used to analyze the correlation between serum NPTX2 and the MMSE score.

RESULTS

The serum NPTX2 level in the control group, normal group and ECD group were 240.00 ± 35.06 pg/mL, 235.80 ± 38.01 pg/mL and 193.80 ± 42.72 pg/mL, respectively. The MMSE score was lowest in the ECD group among the three, while no significant difference was observed between the control and normal groups. In epilepsy patients with cognitive dysfunction, NPTX2 level had a positive correlation with the MMSE score (r = 0.367, P = 0.0253) and a negative correlation with epilepsy duration (r = −0.443, P = 0.0061) and the EEG slow wave/fast wave frequency ratio value in the temporal region (r = −0.339, P = 0.039).

CONCLUSION

Serum NPTX2 was found to be related to cognitive dysfunction and the EEG slow wave/fast wave frequency ratio in patients with epilepsy. It is thus a potential biomarker for the diagnosis of cognitive impairment in patients with epilepsy.

Key Words: Serum neuronal pentraxin 2; Cognitive dysfunction; Epilepsy; Electroencephalogram slow wave/fast wave frequency ratio; Biomarker

Core Tip: Here, we found serum neuronal pentraxin 2 (NPTX2) levels were found to be significantly higher in the normal group than in the cognitive dysfunction group. Additionally, NPTX2 levels showed a positive correlation with cognitive function scores and a negative correlation with epilepsy duration and electroencephalogram (EEG) slow wave/fast wave frequency ratio values in the temporal region. Serum NPTX2 level and the EEG slow wave/fast wave frequency ratio value had good sensitivity and specificity for evaluating cognitive dysfunction. These findings suggest that serum NPTX2 could be a valuable biomarker for diagnosing cognitive impairment in patients with epilepsy, providing important insights for clinical practice.

Citation: Huang XF, Xu MX, Chen YF, Lin YQ, Lin YX, Wang F. Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalogram slow wave/fast wave frequency ratio in epilepsy. *World J Psychiatry* 2023; 13(10): 714-723
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/714.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.714

INTRODUCTION

Epilepsy is a common neurological disorder characterized by abnormal synchronous firing of neurons in the brain[1]. The causes of epilepsy are sometimes known and sometimes unknown (idiopathic epilepsy). Epidemiological studies have shown that approximately 70% of adults with epilepsy have cognitive dysfunction[2,3]. However, there are no effective cognitive assessment criteria for patients with epilepsy. Cognitive dysfunction in epilepsy patients occurs on multiple levels, including executive ability, attention, language, and memory ability. Various epilepsy-related factors are closely related to cognitive dysfunction, including epilepsy course, lesion location, underlying neuropathology, and antiepileptic seizure drugs[2]. Cognitive impairment is common in epileptic patients and is characterized by impairment in neurological function. Due to the lack of early diagnostic methods for cognitive impairment in epilepsy patients, unavoidable neurological damage is present in epilepsy patients[3,4].

Neuronal pentraxin 2 (NPTX2), also named "neuronal activity-regulated pentraxin", is first find in in 1995[5]. NPTX2 is being found to take part in neurotransmission, the maintenance of synaptic plasticity, and the formation of excitatory synapses at presynaptic and postsynaptic sites[6,7]. NPTX2 is also being found to take part in Parkinson's disease[8,9], ischemic diseases[10,11], and Alzheimer's disease[12,13]. A recent study reported that NPTX2 was a novel biomarker for Alzheimer's disease[14]. In addition, researchers have explored the role of NPTX2 in vascular dementia. A recent study reported significantly higher serum levels of NPTX2 in patients with vascular dementia than in healthy controls. Furthermore, NPTX2 serum levels were found to be significantly correlated with cognitive function scores in patients with vascular dementia[15]. However, we still known nothing about NPTX2 in epilepsy.

This study evaluated NPTX2 serum levels in epilepsy patients, and future study their relationship with the patients' cognitive function.

MATERIALS AND METHODS

Patients and ethical statement

This study enrolled 111 patients diagnosed with epilepsy at the First Affiliated Hospital of Fujian Medical University between January 2020 and December 2021. In addition, 30 healthy volunteers were recruited as a control group. The

inclusion criteria were as follows: (1) Clinically confirmed epilepsy [electroencephalogram (EEG) with or without epileptiform discharge]; (2) No seizures 24 h before enrollment; (3) Age between 18 and 60 years; (4) Clear consciousness and cooperative during the examinations; (5) Normal vision, hearing, and speech functions; (6) An education level of at least primary school and an ability to understand the scale content sufficiently to answer the questions; (7) Signed an informed consent form; and (8) Asymptomatic epilepsy (head computed tomography or magnetic resonance imaging does not show intracranial lesions). The exclusion criteria were as follows: (1) Liver dysfunction (alanine transaminase or aspartate aminotransferase > 50 U/L) or renal impairment (serum creatinine > 135 μmol/L); (2) In the acute stage of the disease course; (3) A long-term history of alcoholism or psychoactive substance abuse or recent use of drugs that could affect cognitive function such as antidepressants, antipsychotics, baclofen, and benzodiazepines; or (4) Uncooperative behavior. The study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the ethics board of the First Affiliated Hospital of Fujian Medical University (No. [2019]274). Informed consent was obtained from all participants.

Cognitive function assessment

The mini-mental state examination (MMSE) scale was used to evaluate cognitive function in all participants. The MMSE scale consists of 30 questions related to cognitive function; each correct answer receives one point. An MMSE scale score of less than 27 indicates cognitive dysfunction in persons with at least a junior high school education[16].

Serum NPTX2 assay

Fasting venous blood was drawn from all participants. The peripheral blood was centrifuged at room temperature to obtain serum, which was then frozen in liquid nitrogen, awaiting further tests. Serum NPTX2 was detected using a Human Neuronal pentraxin-2 (NPTX2) enzyme-linked immunosorbent assay kit (CSB-EL016030HU; CUSABIO, Houston, TX, United States).

EEG test

All patients with epilepsy were subjected to an EEG test. The test was conducted in a quiet room, and the patients were told to relax and stay awake with closed eyes. The patients were also subjected to induction tests such as opening their eyes and hyperventilation. The EEG detection parameter settings were as follows: Filter channel 0.5–30 Hz, time constant 0.3, paper feed speed 3 cm/s, gain 100 μV = 1 cm, and scalp resistance of each electrode not exceeding 5,000 Ω. After selecting monopolar lead tracing for 1 min and once the EEG signal was stable, the EEG signal sampling without artifacts and representing EEG background activity was selected. Each patient took 8 s for one sampling unit, with 10 sampling units selected intermittently. The EEG slow wave/fast wave frequency ratio (EEGs value) was calculated using the fast Fourier transform method: EEGs value = (δ+θ)/(α1+α2+β1+β2). δ (1.0–3.9 Hz), θ (4.0–7.9 Hz), α1 (8.0–10.0 Hz), α2 (10.1–13.9 Hz), β1 (14.0–19.9 Hz), and β2 (20.0–30.0 Hz).

Statistical analysis

Data were recorded in an Excel sheet and were analyzed using SPSS 25.0 (IBM, Corp., Armonk, NY, United States). Count data were expressed as percentages, while continuous data were expressed as mean ± SD. The Kolmogorov–Smirnov test was used to test whether the quantitative data were normally distributed. Normally distributed data were presented as (mean ± SD), and differences between groups were analyzed using unpaired Student's *t*-test. Non-normally distributed quantitative data were presented as the median (interquartile range), and differences between groups were analyzed using the Mann–Whitney U-test. The Pearson correlation coefficient was used to analyze the correlation between two variables of measurement data. Furthermore, the receiver operating characteristic curves were constructed, and the area under the curve (AUC) was calculated to assess the performance of NPTX2 serum levels and EEGs values in diagnosing cognitive dysfunction in patients with epilepsy. A P value < 0.05 was considered statistically significant.

RESULTS

Cognitive function and baseline data of patients with epilepsy

Cognitive function was assessed using the MMSE scale. The epilepsy patients with cognitive dysfunction (ECD) group recorded the lowest MMSE score among the three groups. Furthermore, no significant difference in MMSE scores was observed between the control and normal groups (P > 0.05, Figure 1). In addition, the age, gender, education and something related to epilepsy between normal group and ECD group are omparable (P > 0.05, Table 1).

Relationship between NPTX2 serum levels and clinical features

No statistically significant difference was observed in NPTX2 serum levels between the control and normal groups (P > 0.05). However, serum NPTX2 levels in normal group were significantly higher than that in the ECD group (P < 0.05, Figure 2). The serum level of NPTX2 was positively related to MMSE score (r = 0.367, P = 0.0253), not to age (r = 0.115, P = 0.497), and negatively related to epilepsy duration (r = -0.443, P = 0.0061, Figure 3) in the ECD group. In addition, no significant differences were found in gender, education level, epilepsy type, epilepsy drug types, or treatment protocol between the ECD and normal groups (Figure 4).

Table 1 Baseline data for epilepsy patients with different cognitive function and healthy volunteers

Variable	Control (*n* = 30)	Epilepsy		*P* value	
		Normal (*n* = 74)	ECD (*n* = 37)	*P*[1]	*P*[2]
Age (yr, mean ± SD)	33.93 ± 9.39	35.27 ± 9.73	34.68 ± 9.50	0.523	0.760
Gender, *n* (%)					
Male	17	48 (64.86)	20 (54.05)	0.434	0.270
Female	13	26 (35.14)	17 (45.95)		
Education level, *n* (%)					
Junior/senior high school	19	46 (62.16)	20 (54.05)	0.911	0.412
University or above	11	28 (27.84)	17 (45.95)		
Epilepsy onset age (yr, mean ± SD)	–	26.15 ± 7.41	25.62 ± 10.52	–	0.760
Epilepsy duration (yr, mean ± SD)	–	9.12 ± 5.60	9.05 ± 4.10		0.948
Epilepsy type, *n* (%)					
Focal	–	20 (27.03)	9 (24.32)	–	0.760
Overall	–	54 (72.97)	28 (75.68)		
Types of epilepsy drugs, *n* (%)					
0–1	–	57 (77.03)	26 (70.27)	–	0.440
2–3	–	17 (22.97)	11 (29.73)		
Epilepsy treatment protocol, *n* (%)					
VPN	–	39 (52.70)	19 (51.35)	–	0.890
No-VPN	–	35 (47.30)	18 (48.65)		

[1]Control group *vs*. epilepsy (normal) group.
[2]Epilepsy (normal) group *vs*. epilepsy patients with cognitive dysfunction group.
ECD: Epilepsy patients with cognitive dysfunction; VPN: Valproate.

Table 2 Comparison of electroencephalogram slow wave/fast wave frequency ratio for different brain regions of epilepsy patients with different cognitive function (mean ± SD)

Area of ECG	Epilepsy		*t*	*P*
	Normal (*n* = 74)	ECD (*n* = 37)		
Frontal region	0.54 ± 0.20	0.65 ± 0.20	2.781	0.006
Central region	0.45 ± 0.18	0.53 ± 0.16	2.441	0.016
Top region	0.39 ± 0.21	0.45 ± 0.16	1.461	0.147
Temporal region	0.39 ± 0.17	0.62 ± 0.13	7.127	< 0.001
Occipital region	0.28 ± 0.13	0.34 ± 0.19	1.827	0.070

ECD: Epilepsy patients with cognitive dysfunction; ECG: Electrocardiogram.

Ratio of EEG slow wave/fast wave frequency in epilepsy patients

Patients in the normal and ECD groups showed different EEG slow wave/fast wave frequency ratios (EEG value). Patients in the normal group recorded lower EEGs values in the frontal, central, top, temporal, and occipital regions than patients in the ECD group. However, significant differences in EEG values were observed only in the frontal, central, and temporal regions ($P < 0.05$, Table 2).

Relationship between NPTX2 serum levels and EEG values

The correlation analysis showed that NPTX2 serum levels in the group were not correlated with EEG values in the frontal or central region ($P > 0.05$). However, NPTX2 serum levels in the group were negatively correlated with the EEG values

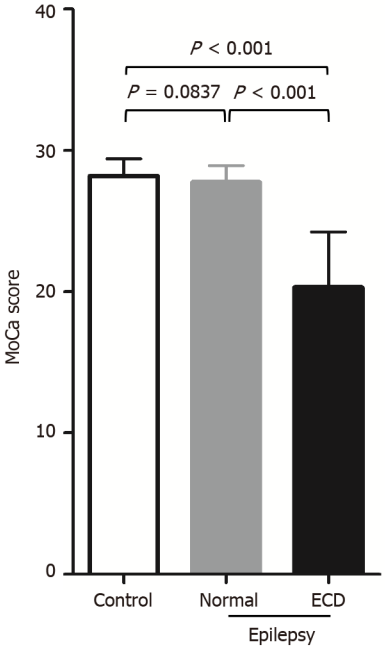

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Figure 1 Mini-mental state examination score of cognitive function among the study participants. Control: Healthy volunteers (*n* = 30); Normal: Epilepsy patients with normal cognitive function (*n* = 74); epilepsy patients with cognitive dysfunction (*n* = 37). ECD: Epilepsy patients with cognitive dysfunction; MoCa: Montreal Cognitive Assessment; MMSE: Mini-mental state examination.

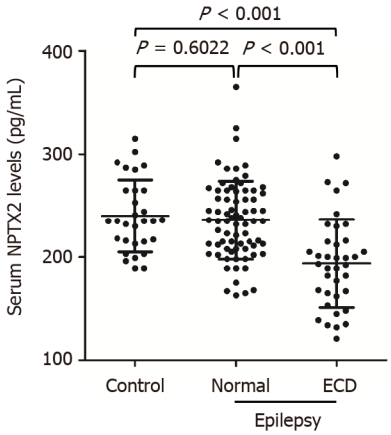

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Figure 2 Serum levels of neuronal pentraxin 2 among study participants. Control: Healthy volunteers (*n* = 30); Normal: Epilepsy patients with normal cognitive function (*n* = 74); epilepsy patients with cognitive dysfunction (*n* = 37). ECD: Epilepsy patients with cognitive dysfunction; NPTX2: Neuronal pentraxin 2.

in the temporal region ($P < 0.05$, Figure 5).

Predictive analysis of NPTX2 serum levels and EEG values of the temporal region in cognitive dysfunction

The AUC value of NPTX2 for diagnosing cognitive impairment in epilepsy patients is 0.777, and the 95%confidence interval (95%CI) is 0.679-0.876 (Figure 6). When the cutoff NPTX2 serum level for distinguishing cognitive function in patients with epilepsy was 206.50 pg/mL, the sensitivity and the specificity was 91.89% and 85.14%, respectively (Figure 6).

Moreover, the AUC value of electrocardiogram (ECG) for diagnosing cognitive impairment in epilepsy patients is 0.815, and the 95%CI is 0.739–0.892 (Figure 6). When the cutoff EEG value for distinguishing cognitive function in patients with epilepsy in the temporal region was set at 0.455, the sensitivity and the specificity was 91.89% and 68.92%, respectively (Figure 6).

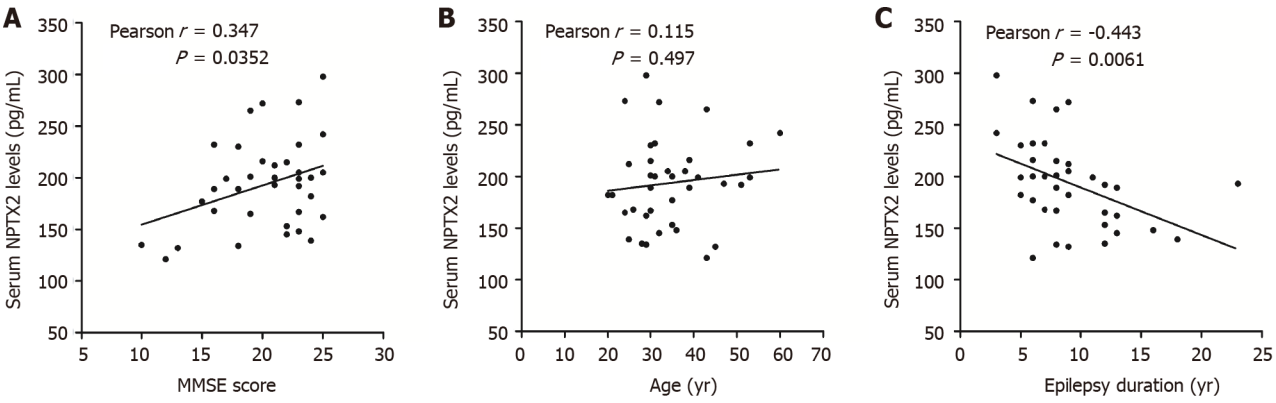

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Figure 3 Correlation between Neuronal pentraxin 2 levels and Mini-mental state examination score, age and epilepsy duration. A to C: Correlation between serum levels of NPTX2 and MMSE score in (A), age (B), and epilepsy duration (C) in epilepsy patients with cognitive dysfunction. NPTX2: Neuronal pentraxin 2; MMSE: Mini-mental state examination.

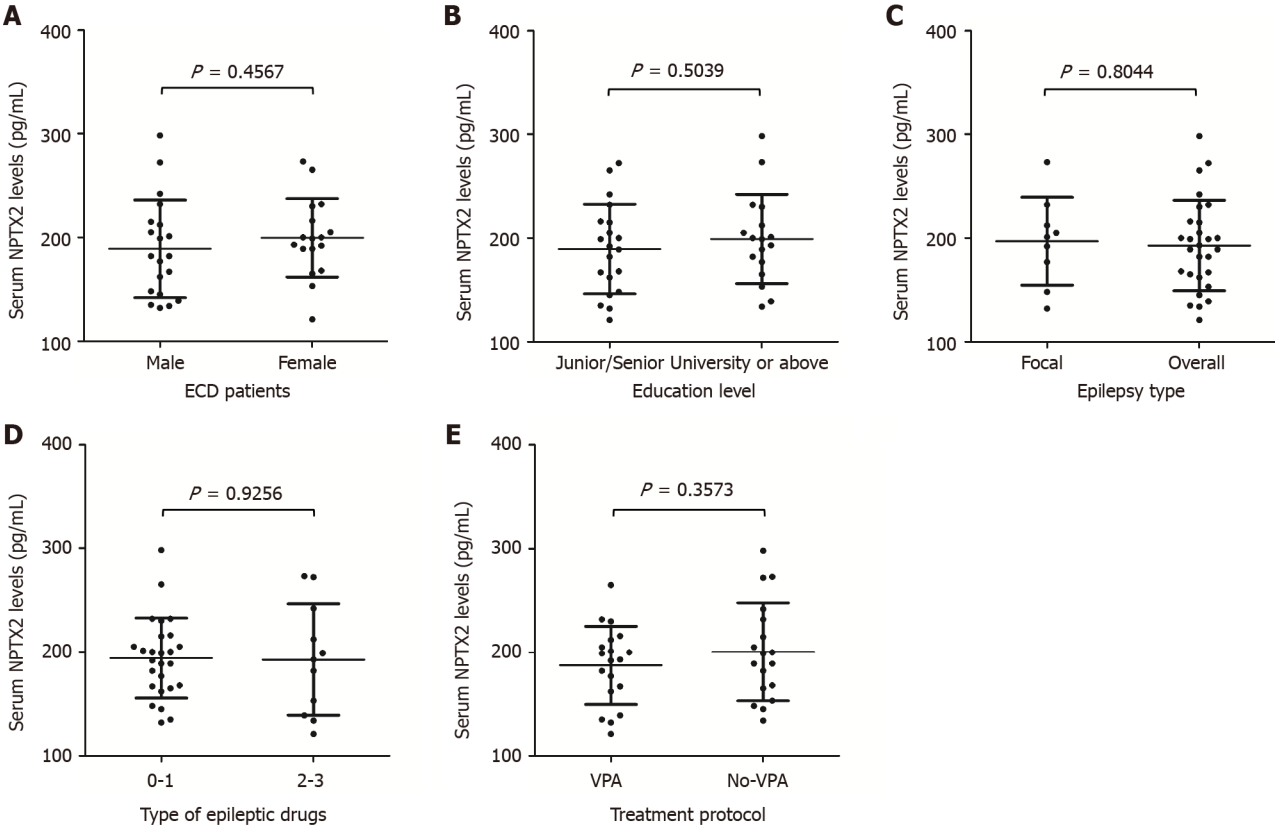

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Figure 4 Comparison between neuronal pentraxin 2 serum levels and different variables in patients with epilepsy and cognitive dysfunction. A to E: Gender(A), education level (B), epilepsy type (C), epilepsy drug types (D), and treatment protocol (E). ECD: Epilepsy patients with cognitive dysfunction; NPTX2: Neuronal pentraxin 2; VPA: Valproate.

DISCUSSION

Epilepsy is a disease that damages the nervous system, causing damage to the patient's nervous system and subsequently leading to cognitive impairment[17,18]. Epilepsy patients with cognitive impairment are affected in various aspects of their lives. However, it can be confirmed that if diagnosed in the early stages of neu-rological damage, existing medicine has the ability to mitigate cognitive impairment caused by epilepsy. Due to the lack of biomarkers for diagnosing neurological damage in epilepsy patients, it is very difficult to diagnose early neurological damage in epilepsy patients, which also leads to varying degrees of cognitive impairment in epilepsy patients as adults. Therefore, there is a need to develop novel biomarkers for the early detection of cognitive impairment in epilepsy patients.

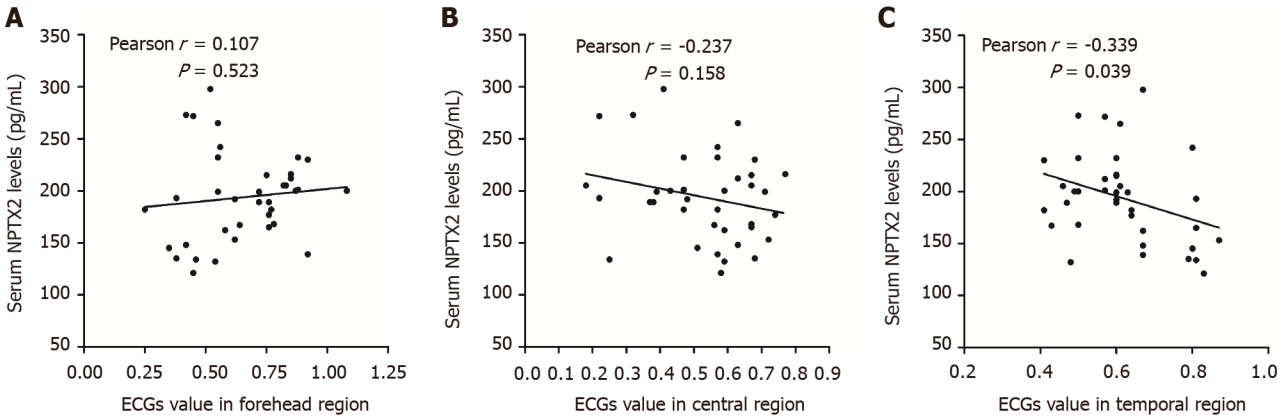

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Figure 5 Relationship between NPTX2 levels and ECG values in different regions. Correlation between NPTX2 serum levels and EEG values in the frontal (A), central (B), and temporal (C) regions of patients with epilepsy and cognitive dysfunction. ECG: Electrocardiogram; NPTX2: Neuronal pentraxin 2.

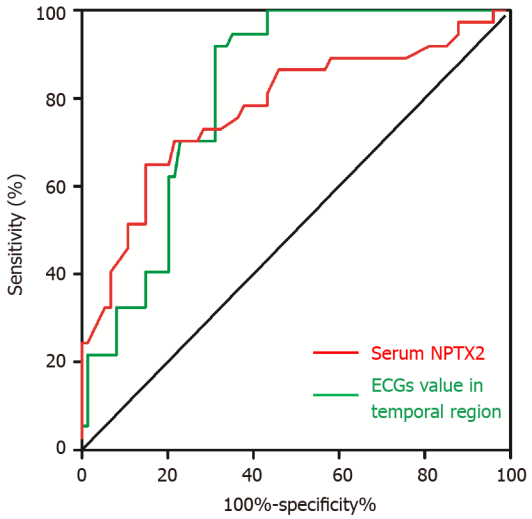

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Figure 6 Receiver operating characteristic curve for predicting serum level values and electroencephalogram values in temporal region in patients with epilepsy and cognitive dysfunction. ECG: Electrocardiogram; NPTX2: Neuronal pentraxin 2.

In this study, we first found that the serum NPTX2 in epilepsy were strongly higher than that in healthy people, and is related to the cognitive function score of epilepsy patients. However, previous studies have shown that NPTX2 is associated with neurological damage, such as significantly accelerating the onset time of Parkinson's mice by upregulating NPTX2 blood levels, and NPTX2 has been identified as associated with neurological damage in Parkinson's patients. In addition, previous studies have also found that the level of NPTX2 in the hippocampus of mice decreases due to cognitive decline caused by neuropathic pain, and it is related to cognitive function in mice after cerebral ischemia[19].

In 1995, NPTX2, a secreted protein, was first discovered[20]. Subsequently, research on NPTX2 was reported, and its main function was mainly studied in synapses, indicating that NPTX2 plays an important role in the nervous system[21, 22]. This function makes NPTX2 associated with the occurrence and development of many neurological diseases, such as stroke, Huntington's disease, and Amyotropic lateral sclerosis[23]. The development and damage of the nervous system are closely related to cognitive function, especially in the hippocampus, and has been reported to have significant expression levels in the cerebrospinal fluid of Alzheimer's disease patients, and it is related to the patient's cognitive function score[24]. In this study, we not only found that the levels of serum NPTX2 in ECD group were lowest, but also found that NPTX2 levels was strongly related to the the patient's cognitive function score. Therefore, these data indicate that NPTX2 is associated with nerve injury and cognitive impairment caused by nerve injury, making it a potential biomarker for diagnosing cognitive impairment in epilepsy patients.

EEG is widely used for diagnosis, identification, prognosis evaluation, and treatment efficacy assessment for neurological diseases, including epilepsy[25]. Quantitative EEG transforms the brain wave signals from the time domain in the ordinary EEG into the frequency domain[26]. Due to the inability to effectively control the onset time and pattern of epilepsy patients, it is very difficult for us to detect the EEG during the seizure period of epilepsy patients. Therefore, researchers usually study the EEG during the interval between seizures[27]. Therefore, we selected EEG in the

background of the interseizure period. This study found lower EEG values in the frontal, central, top, temporal, and occipital regions of patients with epilepsy and normal cognitive function than in those with epilepsy and cognitive dysfunction. Importantly, this study also found that NPTX2 serum levels were negatively correlated with EEG values in the temporal region of patients with epilepsy and cognitive dysfunction. These findings suggest that NPTX2 serum levels and temporal region's EEG values is related to cognitive impairment in epilepsy patients.

This study has several limitations. First, this study was conducted in a single center, and had a low sample size. Second, we did not monitor NPTX2 serum levels dynamically. Third, several factors that could affect NPTX2 serum levels—such as smoking, alcohol use, and drug use history—were not considered. Finally, our patient follow-up period was short.

CONCLUSION

In this study, we found that NPTX2 levels in epilepsy patients were lower than those in the healthy population and were associated with cognitive function scores, seizure duration, and ECG values in epilepsy patients. All in all, these results indicate that serum NPTX2 levels are potential biomarkers for diagnosing cognitive dysfunction in epilepsy patients.

ARTICLE HIGHLIGHTS

Research background

Cognitive dysfunction is a common complication in epileptic patients, but there is a lack of effective diagnostic biomarkers. This study investigated the relationship between serum levels of neuronal pentraxin 2 (NPTX2), an important molecule involved in neurotransmission and synaptic plasticity, and cognitive dysfunction in epilepsy patients. The study also explored the association between electroencephalogram (EEG) slow wave/fast wave frequency ratio and cognitive impairment. The aim was to determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in epilepsy patients, addressing the need for reliable diagnostic tools in this population.

Research motivation

The high incidence of cognitive dysfunction in epileptic patients highlights the need for effective diagnostic biomarkers. Currently, there is a lack of reliable tools to identify cognitive impairment in this population. This study aimed to investigate the correlation between serum NPTX2 levels and EEG slow wave/fast wave frequency ratios with cognitive dysfunction in epilepsy patients. By exploring these potential biomarkers, the study aimed to contribute to the development of a diagnostic tool for identifying cognitive impairment in epilepsy patients, facilitating early intervention and improved patient care.

Research objectives

The main objectives of this study were to investigate the relationship between serum levels of NPTX2 and EEG with cognitive dysfunction in epilepsy patients. The study aimed to determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in patients with epilepsy. Additionally, the study aimed to assess the correlation between serum NPTX2 levels, EEG patterns, and cognitive function using the mini-mental state examination (MMSE) scale. The ultimate goal was to contribute to the development of effective diagnostic tools for identifying cognitive impairment in epilepsy patients.

Research methods

The study enrolled three groups of participants: Normal group, 74 epilepsy patients without cognitive dysfunction; epilepsy patients with cognitive dysfunction group, 37 epilepsy patients with cognitive dysfunction; Control group, 30 healthy individuals. Cognitive function was evaluated using the MMSE scale. Serum levels of NPTX2 were measured using an enzyme-linked immunosorbent kit, and EEG recordings were used to calculate the slow wave/fast wave frequency ratio in different EEG regions. Statistical analyses were performed to compare variables among the groups and assess correlations between biomarkers and cognitive function. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of serum NPTX2 and EEG patterns for cognitive dysfunction in epilepsy patients.

Research results

The study found no significant differences in age, gender, or education level among the three groups. There were also no significant differences in epilepsy-related factors between the normal group and the cognitive dysfunction group. Serum levels of NPTX2 were significantly higher in the normal group compared to the cognitive dysfunction group, while the control group showed no significant difference from the normal group. The cognitive dysfunction group had the lowest MMSE scores. The EEG slow wave/fast wave frequency ratio values were significantly higher in the cognitive dysfunction group compared to the normal group in various EEG regions. In epilepsy patients with cognitive dysfunction, NPTX2 levels correlated positively with the MMSE score and negatively with epilepsy duration and the EEG slow wave/fast wave frequency ratio value in the temporal region. ROC curve analysis demonstrated that serum NPTX2

level and EEG patterns had diagnostic potential for evaluating cognitive dysfunction in epilepsy patients.

Research conclusions

The study concluded that serum NPTX2 levels are associated with cognitive dysfunction and the EEG slow wave/fast wave frequency ratio in epilepsy patients. Serum NPTX2 shows potential as a diagnostic biomarker for cognitive impairment in epilepsy. The study found no significant differences in demographic and epilepsy-related factors between the normal and cognitive dysfunction groups. However, serum NPTX2 levels were significantly higher in the normal group compared to the cognitive dysfunction group. The EEG slow wave/fast wave frequency ratios were also higher in the cognitive dysfunction group. These findings suggest that serum NPTX2 and EEG patterns may serve as valuable indicators for diagnosing cognitive impairment in epilepsy patients.

Research perspectives

The findings of this study highlight the potential of serum NPTX2 as a diagnostic biomarker for cognitive impairment in epilepsy patients. Further research is needed to validate and expand upon these results. Future studies could explore the underlying mechanisms linking NPTX2 levels and cognitive dysfunction, investigating the role of NPTX2 in neurotransmission and synaptic plasticity. Additionally, larger sample sizes and longitudinal studies could provide more robust evidence regarding the relationship between serum NPTX2, EEG patterns, and cognitive dysfunction. Ultimately, establishing reliable biomarkers could aid in early detection and intervention for cognitive impairments in epilepsy, improving patient outcomes and quality of life.

FOOTNOTES

Author contributions: Huang X, Lin Y, and Wang F were responsible for the study's conception and design; Xu M and Chen Y provided administrative support; Huang X and Lin Y provided the study materials and patients; Xu M and Lin Y conducted data collection; Chen Y and Wang F conducted data analysis and interpretation; all authors contributed to the manuscript writing process and granted final approval for the manuscript.

Supported by 2022 Educational Research Program for Young and Middle-aged Teachers in Fujian Province (Science and Technology), No. JAT220107.

Institutional review board statement: The study was approved by the ethics board of First Affiliated Hospital of Fujian Medical University (No. [2019]274).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Wu RR

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