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Influencing factors for cognitive impairment in patients with dorsolateral frontal lobe epilepsy

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Abstract

Background & Objective: To explore the influencing factors for cognitive impairment in patients with dorsolateral frontal lobe epilepsy (FLE) and the correlation between cognitive function and abnormal electroencephalograms. *Methods:* Eighty-two patients with dorsolateral FLE treated from April 2018 to April 2020 were selected. According to cognitive function test results, they were divided into a normal group (n=47) and an impairment group (n=35). Their general data were compared. The factors affecting cognitive function were assessed by univariate and multivariate logistic regression analyses. A nomogram prediction model was constructed for predicting cognitive impairment, and the predictive accuracy was assessed. The cognitive function and electroencephalogram results were compared. The correlation between abnormal electroencephalograms and cognitive function was analyzed. *Results:* Onset age ≥20 years old, educational years ≤12 years, course of disease ≥8 years, seizure frequency ≥once every 4 months, seizure duration ≥1.5 min and medication type were independent risk factors influencing the cognitive function of patients with dorsolateral FLE. The nomogram prediction model was highly accurate for predicting cognitive impairment. The levels of directional memory, associative learning memory, free recall of images, re-recognition of meaningless images, recall of character features, digital symbol substitution test, verbal fluency test, and backward digital span test of the impairment group were significantly lower than those of the normal group, and the number of patients with abnormal electroencephalograms was remarkably larger in the former group. Abnormal electroencephalogram had a significant negative correlation with cognitive impairment. *Conclusion:* Onset age, educational years, course of the disease, seizure frequency, seizure duration and medication type influence the cognitive function of patients with dorsolateral FLE. Abnormal electroencephalograms are closely correlated with cognitive function.

Keywords: dorsolateral frontal lobe epilepsy; cognitive function; electroencephalogram; correlation; prediction model

INTRODUCTION

Frontal lobe epilepsy (FLE) is a group of epilepsy syndromes occurring in the frontal lobe, with an incidence rate second only to that of temporal lobe epilepsy.[1] It is clinically characterized by short duration, onset during sleep, and excessive exercise.[2] As the frontal lobe is the center of advanced nervous activities with a complex anatomical structure and function, the symptoms of frontal lobe impairment include voluntary movement, verbal command voluntary movement, visual cognitive process, and intelligence disorders.[3] The clinical manifestations of FLE are diverse, special, and mostly symptomatic, which are closely associated with functional regions such as the motor center, verbal center, and lateral optic center.[4] FLE patients have the characteristics of focal seizure with or without impaired awareness and focal to bilateral tonic-clonic seizure[5], which may result in misdiagnosis, thus delaying treatment and affecting the prognosis of patients. With the development of neuroimaging and electrophysiology, it is now well-established that the epileptic foci of FLE include the dorsolateral frontal lobe, frontal cortex, supplementary motor region, and anterior parts of the cingulate gyrus.[6] In most cases, dorsolateral FLE is dominated by tonic seizures accompanied by head-eye deflection, speech pauses, visual hallucination, and illusion or compulsive thinking.[7] In this

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study, therefore, the influencing factors for the cognitive impairment of patients with dorsolateral FLE and the correlation between cognitive function and abnormal electroencephalograms were investigated.

METHODS

General data

Eighty-two subjects with dorsolateral FLE treated in our hospital from April 2018 to April 2020 were selected, including 51 males and 31 females. Electroencephalogram characteristics of FLE: 1) Pathological discharges dominated by the frontal area, some of which tended to spread to temporal and central areas; 2) the discharges were mainly unilateral, sometimes spreading to both sides; 3) explosive electrical activity occurred in the frontal area upon attack and suddenly stopped.

They were divided into a normal group (n=47) and an impairment group (n=35) according to the scores of the Mini-Mental State Examination (MMSE).[8] An MMSE score of ≥27 points was defined as normal, and an MMSE score of <27 points was determined as impairment. The normal group consisted of 30 males and 17 females, with an average age of (18.64±7.82) years old. The impairment group included 21 males and 14 females, with an average age of (23.85±10.31) years old.

This study has been approved by the ethics committee of our hospital, and all the family members of the subjects have signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria were set as follows: 1) patients conforming to the classification standard of epilepsy and epilepsy syndromes revised by the International League Against Epilepsy (ILAE) in 2017, and with the typical clinical manifestations of dorsolateral FLE (tonic or less common clonus, accompanied by eye and head rotation and speech arrest) and ictal or interictal epileptic discharges in the frontal lobe shown in electroencephalography. Electroencephalography in the paroxysmal period displayed that the electrode in the premotor zone (F3/F4) first showed synchronous, rhythmic, high-amplitude intermittent discharge superimposed by low-amplitude fast rhythm; 2) those who cooperated in cognitive function tests and electroencephalography examinations; 3) those who had complete clinical data.

Exclusion criteria: 1) Patients with various non-epileptic seizures; 2) those who did not cooperate in relevant examinations; 3) those with other types of seizures; 4) those who took medications affecting cognitive function recently; 5) those with long-term alcohol consumption history.

Collection of general data

After admission, the onset age, trauma history, convulsion history, family history, years of education, course of the disease, seizure frequency, and seizure duration of the patients were obtained, their gender and medication types were recorded, and their seizure types were assessed.

Electroencephalography

A full-digital 32-channel video electroencephalogram monitoring system (Nicolet Company, USA) was employed for 24-h tracing according to the 10-20 international system of electrode placement.

Cognitive function tests

The patients' memory functions, including directional memory, associative learning memory, free recall of images, re-recognition of meaningless images, and recall of character features, were detected using the clinical memory scale.[9] According to the original total score and age, the age scale scores of the five items were calculated. Lower scores mean severer memory function impairment.

Then the digital symbol substitution test (DSST) was carried out to evaluate the information processing speed. A lower score indicates slower information processing.

Subsequently, the verbal fluency test (VFT) was utilized to examine the verbal function. A lower score means poorer verbal function.

Finally, the working memory function was tested using the digital span (DS) scale which included the forward and backward repeating of numbers. A lower score suggests poorer working memory function.

Construction of nomogram prediction model

The factors influencing the cognitive function of patients with dorsolateral FLE were assessed by multivariate logistic regression analysis, and the variables exhibiting significant differences were assigned. Next, a nomogram prediction model was constructed by R software (R3.3.2) and the RMS software package.

Statistical analysis

SPSS 19.0 software was utilized for statistical analysis, and GraphPad Prism 5.0 software was employed for plotting. The differences were compared by the *t-test* between two groups, and the differences in the percentage and composition ratios were compared among multiple groups by the χ^2 test. Univariate and multivariate logistic regression analyses were performed for the factors influencing cognitive function, and the accuracy of the nomogram model for predicting cognitive impairment was evaluated using a calibration curve. P<0.05 represented that a difference was statistically significant.

RESULTS

General data

The onset age, educational years, course of the disease, seizure frequency, seizure duration, and medication types of the two groups were significantly different (P<0.05), but the other general data were similar (P>0.05) (Table 1).

According to univariate logistic regression analysis, the age of onset [odds ratio (*OR*)=2.743, 95% confidence interval (*95%CI*)=1.985-3.501, P=0.001], educational years (*OR*=3.417, *95%CI*=2.694-4.140, P<0.001), seizure frequency (*OR*=4.128, *95%CI*=3.425-4.831, P<0.001), seizure duration (*OR*=3.742, *95%CI*=3.064-4.420, P<0.001) and medication types (*OR*=3.125, *95%CI*=2.437-3.813, P<0.001) were associated with the cognitive impairment in patients with dorsolateral FLE. Meanwhile, the multivariate logistic regression analysis results revealed that onset age ≥20 years old, educational years ≤12 years, course of disease ≥8 years, seizure frequency ≥once every 4 months, seizure duration ≥1.5 min and medication types were independent risk factors influencing the cognitive function of patients with dorsolateral FLE (Table 2).

Construction of nomogram prediction model

Based on the results of the multivariate logistic regression analysis, a nomogram model was constructed for predicting the cognitive impairment in patients with dorsolateral FLE using R software. Twenty points were assigned for onset age ≥20 years old, 24 points for educational years ≤12 years, 35 points for course of disease ≥8 years, 28 points for seizure frequency ≥once every 4 months, 30 points for seizure duration ≥1.5 min, and 26 points for 3 types of medications. The total score was 163 points, and the corresponding

Table 1: General data

Group	Normal group (n=47)	Impairment group (n=35)	t/χ^2	P
Male/female	30/17	21/14	0.003	0.956
Age of onset (years old)	18.64±7.82	23.85±10.31	2.603	0.011
Trauma history [n (%)]	6	8	0.021	0.884
History of convulsion [n (%)]	5	2	0.005	0.943
Family history [n (%)]	1	1	0.002	0.992
Educational years (years)	13.64±4.96	10.42±3.82	3.197	0.002
Course of disease (years)	5.58±2.38	11.37±6.42	5.690	0.000
Seizure frequency	3.25±0.89	5.26±1.27	8.428	0.000
Seizure duration (min)	1.24±0.53	1.72±0.75	3.397	0.001
Seizure characteristic [n (%)]			8.741	0.000
focal aware seizure	5	4	-	-
focal impaired awareness seizure	4	3	-	-
focal to bilateral tonic-clonic seizure	38	28	-	-
Type of medication [n (%)]			12.314	0.025
None	24	15	-	-
One type	17	9	-	-
Two types	5	6	-	-
Three or more types	1	5	-	-

Univariate and multivariate logistic regression analysis results of factors affecting cognitive function

Table 2: Univariate and multivariate logistic regression analysis results of factors affecting cognitive function

Item	Univariate analysis		P	Multivariate analysis		P
	OR	*95%CI*		*OR*	*95%CI*	
Onset age ≥20 years old	2.743	1.985~3.501	0.001	2.585	1.742~3.428	0.028
Educational years ≤12 years	3.417	2.694~4.140	0.000	3.285	2.637~3.933	0.016
Course of disease ≥8 years	4.675	3.958~5.392	0.000	4.462	3.719~5.205	0.000
Seizure frequency ≥once every 4 months	4.128	3.425~4.831	0.000	3.984	3.126~4.842	0.004
Seizure duration ≥ 1.5 min	3.742	3.064~4.420	0.000	3.418	2.937~3.899	0.002
Type of medication	3.125	2.437~3.813	0.000	2.879	2.120~3.638	0.008

incidence rate of dorsolateral FLE was 42.68% (Figure 1).

Accuracy evaluation of nomogram prediction model

The calibration curve was used to assess the accuracy of the nomogram model for predicting the cognitive impairment of patients with dorsolateral FLE. The calibration curve and standard reference line were highly consistent, which revealed that the incidence rate of cognitive impairment predicted by the nomogram prediction model was in accordance with the actual one, indicating high predictive accuracy (Figure 2).

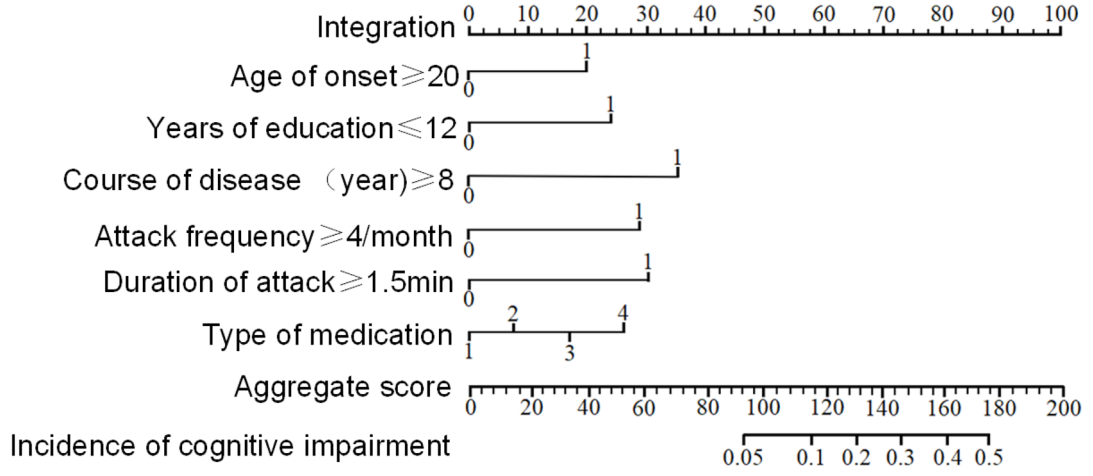

Figure 1. Construction of the nomogram prediction model.

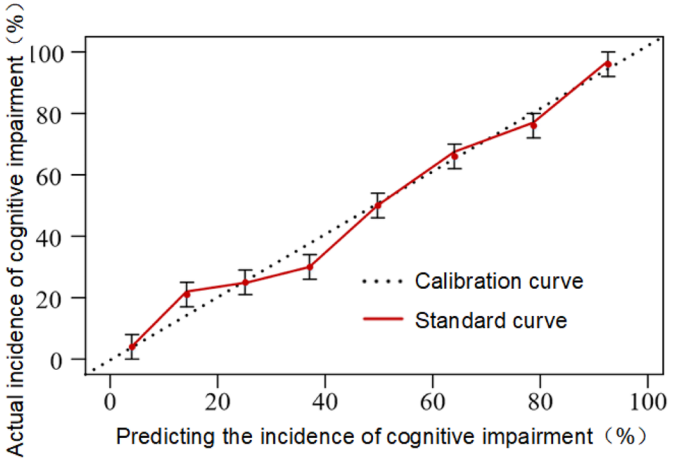

Figure 2. Calibration curve of a nomogram prediction model.

Cognitive function test results

The levels of directional memory, associative learning memory, free recall of images, re-recognition of meaningless images, recall of characters, DSST, VFT and backward DS test of the impairment group were significantly lower than those of the normal group (P<0.05), but the two groups had similar forward DS test levels (P<0.05) (Table 3).

Electroencephalogram results

The normal group had significantly more patients with normal electroencephalograms and fewer patients with abnormal electroencephalograms than the impairment group (P<0.05) (Table 4).

Abnormal electroencephalograms were significantly negatively correlated with directional memory, associative learning memory, free recall of images, re-recognition of meaningless images, recall of character features, DSST, VFT and backward DS test levels in patients with dorsolateral FLE (P<0.05) (Table 5).

DISCUSSION

FLE ranks second only to temporal lobe epilepsy in the incidence rate, accounting for about

Table 3: Cognitive function test results

Group	Normal group (n=47)	Impairment group (n=35)	*t*	P
Directional memory	19.47±4.83	12.75±4.58	6.370	0.000
Associative learning memory	23.65±8.93	14.72±5.60	2.185	0.032
Free recall of images	21.85±5.02	15.41±4.71	5.898	0.000
Re-recognition of meaningless images	18.97±5.94	13.17±5.13	4.631	0.000
Recall of character features	18.77±6.58	10.78±5.16	5.947	0.000
DSST	57.31±14.62	44.45±12.66	4.168	0.000
VFT	44.88±9.13	34.85±8.64	5.033	0.000
Forward DS test	8.61±1.31	8.33±1.20	0.992	0.324
Backward DS test	6.12±1.98	4.83±1.69	3.103	0.003

Table 4: Interictal electroencephalogram results [n (%)]

Group	Normal group (n=47)	Impairment group (n=35)	χ^2	P
Normal electroencephalograms	30 (63.83)	3 (8.57)		
Epileptiform discharge in electroencephalograms	4 (8.51)	19 (54.29)	34.354	0.000
Slow-wave discharge in electroencephalograms	13 (27.66)	13 (37.14)		

Correlation between cognitive function and abnormal electroencephalograms in patients with dorsolateral FLE

Table 5: Correlation between cognitive function and abnormal electroencephalograms in patients with dorsolateral FLE

Indicator of cognitive function test	Partial regression coefficient *B*	Standard error s_B	Standard partial regression coefficient β	*t*	P
Directional memory	-19.875	7.624	-0.290	-2.875	0.028
Associative learning memory	-30.418	8.316	-0.385	-3.186	0.014
Free recall of images	-42.185	10.872	-0.428	-2.428	0.002
Re-recognition of meaningless images	-22.480	8.265	-0.542	-2.673	0.000
Recall of character features	-28.073	11.062	-0.314	-4.289	0.005
DSST	-33.615	12.183	-0.435	-3.652	0.032
VFT	-35.182	12.478	-0.369	-3.184	0.001
Backward DS test	-20.460	8.139	-0.405	-3.825	0.000

20-30% of all types of focal epilepsy.[10,11] The frontal lobe is the largest brain lobe and also the latest brain structure in phylogenesis and ontogenesis, accounting for about 36% of the whole human brain capacity.[12] It also contains many vital centers, with complex anatomical structure and function, which can be roughly divided into the dorsolateral frontal lobe, basal frontal lobe and medial frontal lobe.[13] The motor symptoms of FLE, including simple movement and complex movement, often occur in the early stage of seizures.[14] The motor symptoms of dorsolateral FLE are associated with the location of epileptogenic zones. Specifically, the motor symptoms of anterior frontal epilepsy are mainly complex movement, those of posterior frontal epilepsy are primarily simple movement with less complex movement, and those of frontal epilepsy in the cross-border epileptogenic zone usually include both simple movement and complex movement.[15] FLE not only leads to common convulsive or non-convulsive clinical seizures but also causes different degrees of cognitive impairment, as a crucial cause for the decline in the quality of life of FLE patients.[16] The main manifestations of cognitive impairment include memory loss, inattention and reduction in the mental movement speed, which can give rise to mental retardation in severe cases. Therefore, identifying and preventing the cognitive impairment of FLE patients in the early stage are of great significance to the improvement of prognosis.

Cognitive function, as a vital indicator for evaluating the quality of life of FLE patients, is related to various mechanisms such as neuronal apoptosis, sleep disorder, epileptiform discharge and abnormal neurotransmitter system.[17] Different epileptogenic foci in FLE patients trigger corresponding cognitive impairment, and those in patients with dorsolateral FLE are divided into pre-central, pre-motor and frontal regions. In the pre-central epileptogenic region, local clonic seizures and localized diffusion occur, accompanied by ipsilateral head deflection and Todd paralysis after seizures. Seizure in the pre-motor epileptogenic region is mainly present as an excessive movement of the proximal joint of the limb. The frontal region mainly regulates advanced brain functions such as decision control, emotional presentation and working memory.[14] Onset age, seizure frequency, seizure duration, course of the disease, seizure types and treatment factors can result in cognitive impairment in epileptic patients.[18] Miller *et al*. reported that the long course of disease increased the possibility of substantial brain damage, thus causing cognitive impairment such as memory loss.[19] Moreover, the educational level has been closely associated with the cognitive impairment in FLE patients, probably due to the correlation between treatment compliance and educational level.[20] In this study, univariate and multivariate logistic regression analyses revealed that onset age ≥20 years old, educational years ≤12 years, course of disease ≥8 years, seizure frequency ≥once every 4 months, seizure duration ≥1.5 min and medication type were independent risk factors influencing the cognitive function of patients with dorsolateral FLE.

Cognitive impairment includes impaired memory, computing power, verbal ability, executive ability and other related abilities. About 30-40% of epileptic patients are accompanied by cognitive impairment to varying degrees.[21] Hence, identifying the cognitive impairment of patients with FLE in the early stage has attracted widespread attention. Currently, the cognitive impairment of FLE patients is mainly evaluated by the neuropsychological test in clinical practice. The clinical working memory scale evaluates the short-term memory of patients with FLE through auditory and visual memory and analyzes the characteristics of cognitive impairment.[22] Besides, DSST, VFT and DS tests are also effective tools for evaluating the cognitive function of FLE patients, which comprehensively detect the information processing speed, verbal function and working memory function of patients, respectively. Neuropsychological tests and other evaluation scales can comprehensively assess the cognitive function of FLE patients, but they are inconvenient and subjective, so it is necessary to prove the cognitive impairment of FLE patients based on electrophysiological changes. Furthermore, electroencephalograms play crucial roles in the clinical diagnosis of epilepsy, detection of the location of epileptic foci, and evaluation of the therapeutic effect on epileptic patients.[23] de Barros Lourenço *et al*. reported that the waveform, discharge location and discharge process in electroencephalograms were closely associated with the cognitive function of epileptic patients.[24] Additionally, there is a significant correlation between the cognitive function of patients with temporal lobe epilepsy and abnormal electroencephalograms.[25] In the present study, the impairment group had significantly lower levels of directional memory, associative learning memory, free recall of images,

re-recognition of meaningless images, recall of character features, DSST, VFT, and backward DS test, but significantly more patients with abnormal electroencephalograms than those of the normal group. Abnormal electroencephalograms had significant negative correlations with the test level of cognitive function of patients.

In summary, onset age ≥20 years old, educational years ≤12 years, course of disease ≥8 years, seizure frequency ≥once every 4 months, seizure duration ≥1.5 min, and type of medication are independent risk factors influencing the cognitive function of patients with dorsolateral FLE. Abnormal electroencephalograms were significantly negatively correlated with the test level of cognitive function of patients with cognitive impairment. The findings provide reference for clinically evaluating the cognitive function of patients with dorsolateral FLE.

DISCLOSURE

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Conflict of Interest: None.

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