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Clinical characteristics of cognitive impairment and its related risk factors in post-stroke epilepsy

Hongling Hou[1,2]*, Guoxian Sun[2]*, Zuowei Duan[2], Lihong Tao[2], Shuai Zhang[2], Qi Fang[1]

[1] Department of Neurology, The First Affiliated Hospital of Soochow University, No. 899, Pinghai Road, Suzhou, Jiangsu 215006, China
[2] The Affiliated Hospital of Yangzhou University, No. 368, Hanjiang Road, Yangzhou, Jiangsu 225012, China

*Authors contributed equally.

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ABSTRACT

Objective. Post-stroke epilepsy (PSE) patients are prone to cognitive impairment (CI) due to multiple factors. This study aimed to assess clinical characteristics of CI and its related risk factors in newly diagnosed Chinese Han adult epilepsy patients with ischaemic stroke.

Methods. Data were collected on PSE patients hospitalized in the neurology ward of the Affiliated Hospital of Yangzhou University, from January 2016 to May 2019. Newly diagnosed PSE patients were followed for six months; their cognitive functions were then assessed according to the Chinese Beijing version of the Montreal Scale (MoCA) and patients were divided into a PSE+CI group (MoCA scale score <26) (n=81) or PSE-CI group (MoCA scale score ≥26) (*n*=36). Data collection tools also included the Chinese versions of the Zheng Self-assessment Anxiety Scale, the Zheng Self-assessment Depression Scale, the Barthel index and the National Hospital Seizure Severity Scale. We compared the basic clinical characteristics between the two groups of patients and investigated the factors of CI in PSE patients.

Results. In total, CI was present in 81 (69%) and absent in 36 (31%) PSE patients. MoCA total score in the PSE+CI group was 20.85±4.13 and 27.53±1.34 in the PSE-CI group. The Bonferroni corrected significance level was 0.0013. Scores for multiple cognitive domains (visuospatial/executive skills, naming, attention, language and delayed recall) were lower in the PSE+CI group than the PSE-CI group. Moreover, the PSE+CI group had a higher incidence of depression and anxiety. Univariate analysis showed that diabetes (p= 0.000) and the number of antiepileptic drugs (AEDs) (p= 0.001) were associated with CI in PSE. Binary logistic regression analysis showed that diabetes (odds ratio [OR]: 5.242, 95% confidence interval [CI]: 1.680-16.363, p= 0.004), high homocysteine levels (OR: 1.103, 95% CI: 1.008-1.207, p= 0.033) and the number of AEDs (OR: 3.354, 95% CI: 1.225-9.180, p= 0.019) were associated with CI in PSE.

Significance. Diabetes, high homocysteine levels and a higher number of AEDs may be risk factors for CI in PSE.

Key words: ischaemic stroke, post-stroke epilepsy, cognition impairment, risk factors

• **Correspondence:**
Qi Fang
Department of Neurology,
The First Affiliated Hospital of Soochow University,
No. 899, Pinghai Road,
Suzhou, Jiangsu 215006, China
<fangqi_008@126.com>

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Approximately 10% of the epilepsy cases worldwide are related to stroke, and this proportion has been found to increase with the age of the population. In one study, the condition was reported in 55% among the elderly (>65 years of age) [1].

According to a survey, there were approximately 13 million Chinese adults above 40 years of age in 2019 who experienced a stroke and 14% of elderly stroke patients suffered from epilepsy [2]. Post-stroke epilepsy (PSE) has been recognized as an important clinical issue in stroke survivors.

The prevalence of post-stroke depression (PSD) is reported at 31.1%, and that of post-stroke anxiety at 20.4% [3]. The incidence of PSD within five years after stroke has been reported at 31% [4]. PSD can occur during the acute phase (<one month), mid-term (one to six months) and recovery phase (>six months) after stroke, with an incidence of 33%, 33%, and 34%, respectively [5]. The presence of cognitive impairment (CI) after stroke was reported in 30% cases, and was related to mortality, disability, and prolonged hospital stay [6]. Patients with PSE often experience various complications, such as CI, depression, and anxiety, which severely affect their quality of life and prognosis and could aggravate strokes, even becoming life-threatening [7]. Witt *et al*. reported frequent CI in patients with epilepsy, and complications were common in elderly patients with untreated new-onset epilepsy [8]. Breuer *et al*. reported that old age and the presence of comorbidities were risk factors for CI in patients with epilepsy [9]. Dabbs *et al*. used multiple magnetic resonance imaging (MRI) techniques to distinguish between subtypes of CI in patients with temporal lobe epilepsy, and suggested that extensive neuroanatomical changes could form the basis of different patterns of cognitive deficits [10]. Van Tulji *et al*. reported that PSE patients had lower mini-mental state examination (MMSE) scores than matched patients with stroke only [11]. To date, most studies have focused on the risk factors in PSE patients [12, 13], and little attention has been paid to cognition, quality of life and prognosis of PSE. Thus, further clarification is required to elucidate the clinical characteristics and risk factors of CI in PSE and affected domains.

In this study, newly diagnosed PSE patients were followed for six months. These patients tended to be stable, often discharged from hospital, and their cognitive functions were easily overlooked. Accordingly, the aim of the present study was to assess clinical characteristics and related risk factors of CI in newly diagnosed Chinese Han adult epilepsy patients with ischaemic stroke. We hypothesized that PSE patients are more likely to have CI, anxiety and depression, and the occurrence of these complications may have an impact on the poor prognosis of these patients.

Methods

Patients

This study was conducted at the Department of Neurology of the Affiliated Hospital of Yangzhou University, China, from January 2016 to May 2019. The study protocol was approved by the Institutional Review Board of the Affiliated Hospital of Yangzhou University. All patients and their families voluntarily provided written informed consent and all information regarding patient identity was encrypted.

In 2014, the International League Against Epilepsy (ILAE) stated that: epilepsy is a disease of the brain defined by any of the following conditions:

- at least two unprovoked (or reflex) seizures occurring >24 hours apart;
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
- diagnosis of an epilepsy syndrome [14]. However, there is no exact definition of PSE. We defined PSE clinically as the occurrence of two recurrent seizures, occurring more than one week after a stroke, not caused by metabolic dysfunction, toxicity, or other factors in patients with a seizure and clear signs of cerebral infarction on imaging (patients without clinical signs of stroke before their seizure were also included), excluding the acute phase of stroke [15].

The inclusion criteria were as follows:

- patients who met the diagnostic criteria for ischaemic stroke (the 4th Chinese Academic Conference for Cerebrovascular Diseases) and PSE (the 1st National Academic Conference for Epilepsy of the Chinese Medical Association);
- patients aged between 30 years and 90 years;
- newly diagnosed PSE patients followed for six months;
- and an National Institutes Of Health Stroke Scale (NIHSS) score of 1-15.

The exclusion criteria were patients with:

- a history of progressive CNS disorders (*e.g.*, Parkinson disease, dementia, demyelinating conditions);
- severe psychiatric conditions (*e.g.*, schizophrenia, bipolar disorder);
- concussion and other traumatic brain injuries;
- substance abuse-related disorders in the previous year;
- severe CI and global aphasia (which may affect the tests and questionnaires);

- patients with recurrent stroke, death, neurodegenerative disease during the follow-up period;
- and patients who failed to cooperate with complete data collection.

In the end, we collected data on 117 patients with PSE and CI (men:women=71:46), and patients were allocated to either the PSE+CI group (MoCA scale score <26) (*n*=81) or PSE-CI group (MoCA scale score ≥26) (*n*=36). Severe CI patients (*n*=19 cases) and global aphasia patients (*n*=21 cases) were excluded.

Study methods

In this study, the demographic data of all patients were collected, including age, sex, education, occupational status, family monthly income, spouse, disease characteristics, auxiliary examinations, and details of AED treatment. All patients underwent face-to-face cognitive assessment and examination by trained neurologists. These tests and interviews were evaluated in the neurology ward. Patients unable or unwilling to travel to the neurology ward were tested at home or at their care facility. Cortical involvement, stroke location, white matter hyperintensity (WMH), and haemorrhagic transformation were analysed by MRI and T2-weighted images within three days of admission, by two radiologists who were blinded to the study. On axial T2-weighted image, WMH was defined as irregular high-intensity signals extending into deep white matter, and its severity was evaluated using the Change Rating Scale (Fazekas Scale) with age-related white matter corrections [16]. In our study, only qualitative analysis without further quantitative analysis was performed.
All participants underwent the relevant scales and questionnaires, six months after the new diagnosis of PSE (MoCA, NIHSS, Barthel Index [BI], Self-Rating Anxiety Scale [SAS], Self-Rating Depression Scale [SDS], National Hospital Seizure Severity Scale [NHS3]).

Study tools

We used the BJ-MoCA scale to evaluate the cognitive status of the included patients. The MoCA scale is simple and easy to implement and is widely used in China. Compared with the MMSE scale, the MOCA scale has better sensitivity and specificity; the sensitivity and specificity of MoCA (<26/30) and MoCA (<22/30) is 0.95 and 0.45 (four studies), and 0.84 and 0.78 (six studies), respectively [6, 17]. The following eight cognitive parameters, with scores ranging from 0 to 30 points, are included in the scale: visuospatial/executive skills, naming, memory, attention, language, abstraction, delayed recall, and orientation. The test results are closely related to the level of education. One point is added to the test score to correct deviation in cases where the duration of education was ≤12 years. The MoCA scale was completed by a well-trained doctor in a quiet ward within 10 minutes. A total score of ≥26 was considered normal, and <26, CI was considered to be present.
We used the BI simultaneously to assess performance in activities of daily living in the included patients. The total score ranges from 0 to 100; the higher the score, the greater the performance in daily living activities.
We used the SAS and SDS to assess whether patients had concurrent symptoms of anxiety and depression. The total score was 20-80 and multiplied by 1.25 as the standard score. The higher the score, the more severe the anxiety or depression. A standard score of <50 reflected no anxiety or depression, 50-59 indicated mild anxiety or depression, 60-69 reflected moderate anxiety or depression, and ≥70 suggested severe anxiety or depression. The cut-off value for this study was ≥50 in order to determine whether respondents had anxiety or depression [18, 19].
We used the NHS3 to evaluate the severity of epilepsy based on clinical trials. The total score ranges from 1 to 27; the higher the score, the more severe the seizure.

Statistical analysis

All analyses were performed using SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA). The Levene's test and Kolmogorov-Smirnov test were used to assess homogeneity of variance and the distribution of continuous data, respectively, with non-parametric and parametric tests applied appropriately. The chi-square test was used to compare frequencies (ordinal and qualitative variables) and the independent sample t-test was employed to compare the means. In total, 24 and 16 comparisons are presented in *table 2 and 3,* respectively. Thus, the Bonferroni post hoc correction was applied to establish a significance level for all statistical tests at 0.0013. Binary logistic regression models were used to estimate the independent predictors of CI in PSE. The results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). *P* values <0.05 were considered statistically significant in regression analysis. All tests were two-sided.

Results

In the study, CI was present in 81 (69%) and absent in 36 (31%) PSE patients. Severe CI patients (*n*=19) and global aphasia patients (*n*=21) were excluded. All 117 PSE patients who met the inclusion and exclusion

▼ **Table 1.** Demographic characteristics of the two groups.

Variable	PSE+CI (*n*=81)	PSE-CI (*n*=36)	t/x2	*p* value
Age (years, mean ± SD)	68.99 ± 10.57	69.92 ± 11.97	0.273	0.273
Gender				
Male (*n* [%])	51 (62.96)	22 (61.11)	0.036	0.849
Female (*n* [%])	30 (37.04)	14 (38.89)		
Education				
Primary and middle school (*n* [%])	31 (38.27)	15 (41.67)	0.839	0.657
High school (*n* [%])	27 (33.33)	9 (25)		
College and higher (*n* [%])	23 (28.40)	12 (33.33)		
Family monthly income (¼)				
<3000 (*n* [%])	24 (29.63)	6 (16.67)	4.237	0.120
3000-5000 (*n* [%])	39 (48.15)	16 (44.44)		
>5000 (*n* [%])	18 (22.22)	14 (38.89)		
Employment status				
Employed (*n* [%])	22(27.16)	14(38.89)	1.609	0.205
Unemployed (*n* [%])	59(72.84)	22(61.11)		
BMI (kg/m2)				
<18.5 (*n* [%])	12(14.81)	5(13.89)	0.440	0.803
18.5-23.9 (*n* [%])	33(40.74)	17(47.22)		
≥24 (*n* [%)])	36(44.44)	14(38.89)		

CI: cognitive impairment; SD: standard deviation; PSE: post-stroke epilepsy; BMI: body mass index.
*$p<0.05$.

criteria underwent MRI examinations and routine EEG monitoring, and 93 underwent long-term scalp video-EEG monitoring. Based on these examinations, 30 (25.64%) patients had focal seizures, 66 (56.41%) had generalized tonic-clonic seizures, 21 (17.95%) had both focal and generalized tonic-clonic seizures, and 82 (70.09%) were admitted to hospital with status epilepticus. All patients were treated with AEDs. A total of 55 patients were on monotherapy, including nine with lamotrigine, 18 with carbamazepine, 15 with oxcarbazepine, and 13 with valproate. In all, 62 patients were receiving combinations of AEDs. At the time of evaluation, 42 (35.90%) patients had been completely seizure-free for at least three months.

Clinical features between the two groups and univariate analysis of risk factors for CI

The PSE+CI group had a mean age of 68.99±10.57 years, and those of the PSE-CI group had a mean age of 69.92±11.97 years. The PSE+CI group comprised 51 (62.96%) males and 30 (37.04%) females, while in the PSE-CI, there were 22 (61.11%) males and 14 (38.89%) females. There were no significant differences in age, gender, education, income, occupation or BMI (*table 1*).

Clinical characteristics of the two groups

In our study, the time from cerebral infarction to onset of seizures ranged from eight days to six years. Due to the large time span, the duration was considered in three segments:

- one week to six months;
- 6-12 months;
- >12 months.

There were no statistically significant differences regarding history of smoking and drinking, coronary heart disease, atrial fibrillation, hyperlipidaemia, chronic obstructive pulmonary disease, blood glucose at admission, homocysteine (HCY), creatinine, uric acid, calcium, lactic acid, albumin, stroke location, progressive stroke, WMH, haemorrhagic transformation, seizure type, epilepsy frequency and time since stroke. However, there were statistically significant differences in diabetes (p= 0.000) and the number of AEDs (p= 0.001) (*table 2*).

▼ **Table 2.** Clinical characteristics of the two groups.

Variable	PSE+CI (*n*=81)	PSE-CI (*n*=36)	t/x2	*p* value
History of smoking (*n* [%])	39 (48.15)	19 (52.77)	0.214	0.644
History of drinking (*n* [%])	34 (41.98)	20 (55.56)	1.850	0.174
Hypertension (*n* [%])	67 (82.72)	23 (63.89)	4.977	0.026
Diabetes (*n* [%])	44 (54.32)	7 (19.44)	12.329	0.000[a]
Coronary artery disease (*n* [%])	15 (18.52)	6 (16.67)	0.058	0.810
Atrial flutter (*n* [%])	22 (27.16)	12 (33.33)	0.461	0.497
Dyslipidaemia (*n* [%])	33 (40.74)	15 (41.67)	0.009	0.925
COPD (*n* [%])	9 (11.11)	5 (13.89)	0.183	0.669
Progressive stroke (*n* [%])	13 (16.05)	7 (19.44)	0.203	0.653
Blood glucose at admission (mmol/L, mean ± SD)	8.24 ± 4.28	7.69 ± 3.89	0.658	0.450
HCY (mmol/L, mean ± SD)	16.84 ± 7.77	11.87 ± 5.07	3.515	0.049
Creatinine (μmol/L, mean ± SD)	88.76 ± 28.03	89.02 ± 18.74	-0.855	0.394
Uric acid (μmol/L, mean ± SD)	441.52±124.41	439.36 ± 150.21	0.081	0.334
Lactic acid (mmol/L, mean ± SD)	3.45 ± 2.31	3.34 ± 2.28	0.240	0.362
Calcium (mmol/L, mean ± SD)	2.15 ± 0.32	2.19 ± 0.27	-0.801	0.016
Albumin (mg/L, mean ± SD)	40.15 ± 6.29	40.31 ± 5.20	-0.136	0.393
WMH (*n* [%])	50 (61.73)	15 (41.67)	4.063	0.044
Haemorrhagic transformation (*n* [%])	18 (28.13)	7(25.93)	1.647	0.199
The affected hemisphere				
Right hemisphere	32(39.5)	19(52.8)	4.291	0.232
Left hemisphere	44(54.3)	14(38.9)		
Both	1(1.2)	2(5.6)		
Posterior circulation	4(4.9)	1(2.8)		
Stroke location (*n* [%])				
Cortex	41 (50.62)	20 (55.56)	0.799	0.671
Subcortical	18 (22.22)	9 (25.00)		
Cortex and subcortical	22 (27.16)	7 (19.44)		
Seizure types				
Bilateral seizures only (*n* [%])	45(55.56)	21(58.33)	1.342	0.511
Focal seizures only (*n* [%])	23(28.40)	7(19.44)		
Both types (*n* [%])	13(16.05)	8(22.22)		
Epilepsy frequency (*n* [%])				
<3 times / 3m	56 (69.14)	30 (83.33)	2.580	0.108
≥3 times / 3m	25 (30.86)	6 (16.67)		
Numbers of AEDs (*n* [%])				
Monotherapy	30 (37.04)	25 (69.44)	10.508	0.001[a]
≥2 AEDs	51 (62.96)	11 (30.56)		
Time since stroke				
1w-6m (1)	37 (45.7)	28 (77.8)	11.840	0.003
6m-12m (2)	26 (32.1)	7 (19.4)		
> 12m (3)	18 (22.2)	1 (2.8)		

CI: cognitive impairment; HCY: homocysteine; COPD: chronic obstructive pulmonary disease; WMH: white matter hyperintensity; AED: antiepileptic drug. w: week; m: month.
[a]Significance following Bonferroni correction; α = 0.0013.

▼ **Table 3.** Comparison of scale assessments between the two groups.

Variable	PSE+CI (*n*=81)	PSE-CI (*n*=36)	t/x2	*p* value
MoCA (score, mean ± SD)	20.85 ± 4.13	27.53 ±1.34	-9.467	0.000[a]
Visuospatial/executive skills	2.84 ± 1.13	4.56 ± 0.65	-8.465	0.000[a]
Naming	2.30 ± 0.87	2.97 ± 0.17	-4.601	0.000[a]
Attention	4.53 ± 1.34	5.47 ± 0.94	-3.808	0.000[a]
Language	2.20 ± 0.78	2.89 ± 0.32	-5.113	0.000[a]
Abstraction	1.69 ± 0.56	1.97 ± 0.17	-2.934	0.004
Delayed recall	1.88 ± 1.32	3.92 ± 1.05	-7.934	0.000[a]
Directional	5.11 ± 0.88	5.58 ± 0.60	-2.924	0.004
NIHSS at time of stroke (score, mean ± SD)	7.27 ± 5.80	7.08 ± 6.14	0.159	0.958
NIHSS at time of study (score, mean ± SD)	6.81± 2.65	6.53± 2.53	0.127	0.202
BI (score, mean ± SD)	59.75± 21.62	62.36 ± 17.67	-0.635	0.527
Anxiety (score, mean ± SD)	57.36±15.25	50.86±11.46	2.284	0.024
Anxiety (*n* [%])	51(62.96)	17(47.22)	2.537	0.111
No anxiety (*n* [%])	30(37.04)	19(52.78)	0.965	0.617
Mild (*n* [%])	18(22.22)	8(22.22)		
Moderate (*n* [%])	19(23.46)	6(16.67)		
Severe (*n* [%])	14(17.38)	3(8.33)		
Depression (score, mean ± SD)	59.94±11.51	52.81±12.83	2.985	0.003
Depression (*n* (%)	63(77.78)	19(52.78)	7.430	0.006
No depression (*n* [%])	18(22.22)	17(47.22)	3.042	0.219
Mild (*n* [%])	17(20.99)	9(25)		
Moderate (*n* [%])	28(34.57)	7(19.44)		
Severe (*n* [%])	18(22.22)	3(8.33)		
NHS3(score, mean ± SD)	13.70±4.32	12.61±4.68	1.231	0.221
NHS3≥13 (*n* [%])	49(60.49)	17(47.22)	1.785	0.182
NHS3<(*n* [%])	32(39.51)	19(52.78)		

CI: cognitive impairment; SD: standard deviation; MoCA: Montreal Cognitive Assessment Scale; NIHSS: National Institutes of Health Stroke Scale; BI: Barthel Index; NHS3: National Hospital Seizure Severity Scale.
[a]Significance following Bonferroni correction; α = 0.0013.

Characteristics between the two groups based on the scales

At the time of evaluation, MoCA total scores for the PSE+CI group (20.85 ± 4.13) were lower than those of the PSE-CI group (27.53 ± 1.34), and scores for multiple cognitive domains (visuospatial/executive skills, naming, attention, language and delayed recall) were lower than those of the PSE-CI group. The BI scores in the PSE+CI group (59.75±21.62) were lower than those of the PSE-CI group (62.36±17.67), and the PSE+CI group showed a higher incidence of depression and anxiety (*table 3*).

Binary logistic regression analysis of CI in patients with PSE

\There were few statistically significant variables following Bonferroni correction due to more independent variables in our study, and we included independent variables with p<0.05 into the regression analysis. Binary logistic regression analysis revealed that the independent risk factors for CI in PSE were diabetes (OR: 5.242, 95% CI: 1.680-16.363, *p*= 0.004), HCY levels (OR: 1.103, 95% CI: 1.008-1.207, *p*= 0.033) and the number of AEDs (OR: 3.354, 95% CI: 1.225-9.180, *p*= 0.019) (*table 4*).

Discussion

The main findings of this study are as follows:
- PSE patients were prone to CI;
- and the independent predictors of CI in patients with PSE were diabetes, HCY levels, and use of a combination of AEDs.

At present, studies on PSE have mainly focused on incidence and risk factors, and there have been few

▼ **Table 4.** Binary logistic regression analysis of CI in patients with PSE.

Variable	β value	wald $\chi 2$	OR (95% confidence interval)	*p* value
Hypertension	0.223	0.134	1,259 (0.379-4.119)	0.714
Diabetes	1.675	0.581	5.242 (1.680-16,363)	0.004*
WMH	0.757	0.548	2.132 (0.728-6,214)	0.167
HCY	0.098	0.046	1.103 (1.008-1.207)	0.033*
Calcium	-0.127	0.891	0.881 (0.154-5.056)	0.887
Number of AEDs	1.210	0.514	3.354 (1.225-9.180)	0.019*
Depression score	0.042	3.474	1.043(0.998-1.089)	0.062
Anxiety score	0.020	1.096	1.020(0.983-1.058)	0.295

CI: cognitive impairment; WMH: white matter hyperintensity; HCY: homocysteine; AED: antiepileptic drug.
*$p<0.05$.

studies on the complications of PSE. Seidenberg *et al*. reported that more than one third of patients with epilepsy had different degrees of CI [20]. The two aforementioned studies indicated that CI was common in neurological conditions and seriously affected the prognosis and quality of life of patients. Stroke-related epilepsy can also result in increased morbidity, longer hospitalization, greater disability at discharge and greater resource utilization [1]. Patients of the PSE+CI group showed a higher level of CI; these patients performed poorly in the neuropsychological MoCA test in multiple domains of cognitive function, especially in terms of visuospatial/executive skills, naming, attention, language and delayed recall. The PSE+CI group had lower BI scores and a higher incidence of depression and anxiety compared to the PSE-CI group; although these data were not statistically different between the two groups, the PSE+CI group was nevertheless more impaired compared with the PSE-CI group (*table 3*). Irreversible brain damage after stroke may lead to epilepsy and CI. In addition, epileptiform discharges may interfere with the transmission of information among normal neurons and change normal synaptic connections and neural circuits. This, in turn, may cause ischaemia and hypoxia of the brain, as well as secondary oxidative stress injury, which leads to apoptosis and necrosis of hippocampal neurons. Loss of these neurons induces mossy fibre sprouting and excitatory neural circuit reorganization, which may subsequently lead to CI [21]. Based on one report, certain damage to the central nervous system or pre-existing brain abnormalities may initially affect cognitive function, with subsequent epilepsy as a "second attack" which further results in deviation from the PSE-CI phenotype [22].

Binary logistic regression models demonstrated that diabetes is a predictor of CI in patients with PSE. Important potential factors that may cause CI and epilepsy in stroke patients could be common risk factors, including vascular risk factors, such as diabetes, hypertension, obesity, smoking and hypomotility. These factors may cause atherosclerosis and accelerate the decline in cognitive ability [23]. High glucose concentration is the main pathological feature of diabetes, which may have toxic effects on neurons in the brain, caused by oxidative stress and osmotic insult. In addition, diabetes may also cause disorders of lipid metabolism, and metabolic disorders of acetylcholine, amyloid, and tau protein have also been shown to be important factors that may lead to neuronal damage and decreased brain reserve function [24]. Insulin receptors in the brain are concentrated in the hippocampus and medial temporal cortex, which are areas that support memory. Cholerton *et al*. reported that insulin affects cognitive function by regulating the levels of the neurotransmitters, acetylcholine and norepinephrine. Acetylcholine is a key neurotransmitter for cognition and memory [25]. Insulin resistance may develop following an imbalance in insulin levels in the body, and the decline of acetylcholine level affects cognition and memory. One of the common pathophysiological changes in diabetes is chronic cerebrovascular dysfunction, which causes ischaemia of the microvascular system and imbalance in endothelial cell function, which leads to chronic cerebral hypoperfusion and abnormal local cerebral blood flow. Thus, the synthesis of cognitive function-related neurotransmitters and proteins is blocked, leading to diminished learning and memory function [26]. Although avoiding vascular risk factors is of benefit to patients with cerebrovascular diseases, it remains unclear whether such changes

could reduce seizures and/or alleviate cognitive decline in patients with epilepsy, and this is an important aspect for future research.

This study also indicates that a high level of HCY is an independent risk factor for CI in patients with PSE. Sachdev *et al*. showed that levels of serum HCY negatively correlated with cognition [27]. Studies by Nilsson *et al*. and Miller *et al*. demonstrated that total serum HCY levels in patients with dementia and mild CI were higher than those of healthy controls, and speculated that HCY might be involved in the development of CI [28, 29]. Our study reveals that PSE patients with CI have higher levels of HCY, suggesting that determining the cut-off value for HCY in PSE patients could be a method to predict occurrence of CI in the future. HCY may increase CI through a variety of mechanisms, including vascular injury, oxidative stress, neurotoxicity and apoptosis, promoting the deposition of β-amyloid polypeptide [30, 31]. HCY is involved in atherosclerosis, platelet aggregation and thrombus formation and was shown to induce neuronal dysfunction by activating the N-methyl-D-aspartate receptor, leading to CI. Zieminska *et al*. reported that HCY overactivates Group I metabotropic glutamate receptors, causing damage to nerve excitability, which in turn leads to hippocampal neuron death and CI [32].

In this study, the number of AEDs was associated with CI in patients with PSE. This finding is similar to that of a previous study, in which CI was associated with more AEDs [33]. A higher number of AEDs was significantly negatively associated with subjective and objective cognition in persons with epilepsy [34]. Tedrus *et al*. found that predictive factors for impairment in multiple cognitive domains were age and use of more than one AED [35]. The results suggest that patients with PSE should be treated with monotherapy as far as possible to avoid the negative effects of combination medications. Li *et al*. reported that, overall, the effect of AEDs on CI was mild in adults with newly diagnosed epilepsy [36]. Other studies have reported that AEDs with known cognitive side effects are not associated with CI, due to the short duration of drug use (less than one month) and the failure to reach a threshold. In addition, patients with PSE had more severe CI due to seizures and adverse drug reactions compared to those with only stroke.

There were certain limitations of this study. First, this was a single-centre study with a small sample size, using the MoCA scale which has relatively low sensitivity to detect single-domain cognitive deficits [6], which may have led to an inaccurate estimate of CI. Moreover, the results of the MOCA scale are greatly affected by education level, and it is possible that some of the content should have been modified according to the cultural background of China. In this study, we mainly aimed to screen patients with CI through the MOCA scale. This scale is sensitive to mild CI, and is conducive to early screening, diagnosis and treatment. However, we only assessed cognitive function using the MOCA scale in our study, which is therefore a limitation. Comprehensive neuropsychological testing is necessary to assess true CI, particularly when examining different cognitive domains. Second, the study did not include any further interventions. Sanchez *et al*. found that levetiracetam (LEV) could improve CI by reversing defects in synaptic transmission and reducing abnormal electrical activity in the brain [37]. However, Dinkelacker *et al*. reported that LEV caused aggressive behaviour. The time from initiation of LEV treatment to the appearance of aggressive behaviour was 3.6 months [38]. The risks and benefits of pharmacological interventions must be evaluated in further clinical trials. Third, the evaluation time may have been a source of heterogeneity. Previous studies have confirmed that there were no significant differences in sensitivity/specificity between short- and long-term assessments of patients with CI [6]. However, the responses of patients to tests could vary with time. Fourth, we enrolled PSE patients who were admitted to the hospital, because this made it easier to obtain clinical data, however, this may also have introduced a selection bias.

Conclusions

Overall, the current study shows that CI was frequent in patients with PSE. The independent predictors of CI in patients with PSE were diabetes, high levels of HCY and AED combinations. We call for more attention to cognitive function, and in particular, early recognition and early intervention, to improve the quality of life and reduce the social burden of PSE patients. ■

Key points:

- Patients with PSE are likely to have CI.
- The independent predictors of CI in patients with PSE are diabetes, high levels of HCY, and AED combinations.
- CI in patients with PSE requires early recognition and early intervention.

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors declare no conflicts of interest.

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TEST YOURSELF

(1) What is the diagnosis of PSE?

(2) What factors are related to CI in PSE?

(3) What are the scales for assessing clinic cognitive function?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.