ORIGINAL RESEARCH

Correlation between cognitive impairment during the acute phase of first cerebral infarction and development of long-term pseudobulbar affect

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Purpose: The relationship between cognitive impairment during the acute phase of first cerebral infarction and the development of long-term pseudobulbar affect (PBA) has not been elucidated. Therefore, in this study, we aimed to determine if cognitive impairment during the acute phase of cerebral infarction will increase the risk of long-term post-infarction PBA.

Patients and methods: This was a nested case–control study using a prospective approach. A consecutive multicenter matched 1:1 case–control study of cognitive impairment cases following acute cerebral infarction (N=26) with 26 sex-, education years-, and age-matched controls. Univariate and multivariate conditional logistic regression analyses were performed to study the clinical features and changes in cognitive domain as well as the risk factors for PBA.

Results: Long-term PBA was independently predicted by low Montreal cognitive assessment (MoCA) scores at baseline. Multivariable regression models showed that post-infarction low MoCA scores remained independent predictors of long-term PBA (odds ratio [OR]=0.72; 95% confidence interval [CI]=0.54–0.95; P=0.018). Among all cognitive disorders, digit span test (DST) scores (OR=0.39; 95% CI=0.16–0.91, P=0.030), StroopC time (OR=1.15; 95% CI=1.01–1.31; P=0.037), and clock-drawing task (CDT) scores (OR=0.62; 95% CI=0.42–0.90; P=0.013) were found to be the independent risk factors for PBA.

Conclusion: Cognitive impairment during the acute phase of cerebral infarction increased the risk of cerebral infarction-induced long-term PBA. Development of PBA was closely associated with executive function, attention, and visuospatial disorder.

Keywords: cognitive impairment, pseudobulbar affect, cerebral infarction, neuropsychological tests, cognitive domain

Introduction

Pseudobulbar affect (PBA) is a disorder of emotional expression characterized by uncontrolled outburst of laughter or crying that lacks an appropriate environmental trigger and may be exaggerated or incongruent with the underlying emotional state. It is different from mood disorders, such as depression and bipolar disorders.[1] It may result from a variety of neurological diseases, such as stroke, amyotrophic lateral sclerosis (ALS), traumatic brain injury, and multiple sclerosis. It most commonly happens after stroke, with an incidence of 11%–52%;[2,3] it is most commonly noted during the 4th–6th week after the stroke,[4] however, at various times of onset. After stroke, the incidence of PBA has been shown to be approximately 15% in the first month, 25% in the second month, and 11% in the 12th month. Post-stroke PBA is more common in females than in males, with cerebral infarction occurring more frequently than cerebral hemorrhage. Pathological crying is most common after stroke, followed by pathological

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laughing and crying (PLC).[5,6] PBA is a common complication of neurological impairment, affecting survival satisfaction, social interaction, and rehabilitation processes in the patients with stroke.[3,7] Hence, knowledge regarding the predictors of PBA after cerebral infarction is particularly important for the early diagnosis of the disease.

The acute manifestation of a stroke is not only hemiplegia but also cognitive impairment in the patients. According to the minimum-mental state examination (MMSE), the incidence of cognitive dysfunction 3 months after stroke ranges from 24% to 39%. However, the incidence of cognitive dysfunction after stroke has been assessed as high as 96% using comprehensive neuropsychological tests.[8] A latest Chinese study has shown that the incidence of post-stroke cognitive impairment (PSCI) is around 81% as measured by the Montreal cognitive assessment (MoCA).[9] An observational study of acute stroke cases in People's Republic of China revealed that cognitive impairment is significantly and positively correlated with hemiplegia,[10] which is known to have a significant effect on the prognosis of patients with stroke. While most of the studies have focused on the finding the association of cognitive impairment with hemiplegia, studies focusing on correlation between cognitive impairment and PBA are scarce.[11] At present, it is still unclear whether cognitive impairment early after stroke is a risk factor for long-term PBA, independent of other well-known medical and demographic predictors.

Therefore, in this study, we aimed to test whether acute cognitive impairment is an independent risk factor for PBA 6 months after stroke. Furthermore, we examined which specific cognitive deficits in the early phase of stroke were associated with PBA.

Patients and methods
Source of patients

A total of 202 patients with first acute cerebral infarction treated at two medical centers in Binzhou district, Shandong Province, People's Republic of China, from September 2015 to January 2016 were recruited in this study. These patients had new clinical symptoms and signs, and infarction was confirmed by brain magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI). We further screened the patients according to the following criteria: 1) first acute infarction occurring within 7 days before admission; 2) age in between 18 and 85 years; 3) responsible foci on imaging were consistent with the clinical symptoms and signs; 4) confirmed presence of normal cognitive function before the disease onset; 5) ability to give consent; and 6) capable

of cooperating with the examinations and participate in the neuropsychological tests.

Patients were excluded from this study if 1) they had severe consciousness disorders, such as coma and delirium; 2) they had a history of cognitive impairment (≥3.6 points in the short form of informant questionnaire on cognitive decline in the elderly); 3) they had any reason (eg, language barrier or movement disorders) that prevented them from completing the neuropsychological examinations; 4) they had suffered from a severe disease of any of the vital organs, such as heart, liver, or kidneys; 5) they had suffered from other neurological diseases (eg, genetic degeneration, brain tumors, encephalitis, demyelination, Parkinson's disease, head trauma, or epilepsy); 6) they suffer from anxiety (>7 Hamilton Anxiety Rating Scale), depression (>8 Hamilton Anxiety Rating Scale), or other psychiatric disorders; or 7) they had a history of drug abuse or medications likely to influence the results (such as hormone replacement therapy). According to 1:1 matched case-control study design, the minimum size for the test was computed with the formula.

One hundred and fifty-seven patients were included in this study. Their baseline clinical data were collected, and they completed MoCA test.

Ethical statement

This study was approved by the Ethics Committee of Binzhou Medical University Hospital and all procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee. All patients provided signed informed content before participating in this study.

Study population

Patients with infarction were divided into two groups according to their MoCA scores: cognitive impairment and noncognitive impairment. Given the significant relationship between MoCA score and educational background reported in previous studies,[12,13] the optimal cutoff points were considered as 14 for illiterate individuals, 20 for individuals with 1–6 years of education, and 25 for individuals with 7 or more years of education.[14] Post-infarction cognitive impairment was considered to be present if the MoCA scores were below the aforementioned critical values. Finally, 109 patients were included in their representative cohorts.

This study was designed as a nested case–control study from a prospective cohort study. All study participants were invited for the follow-up assessment; the median follow-up

period was 6 months. We conducted follow-up visits via phone or by outpatient visit using questionnaires to collect the data. After excluding patients with recurrent stroke, unavailable contact information, refusal to participate, and with severe complications, a total of 96 participants (88.0%) (or their guardians) were identified and subsequently agreed to be interviewed as part of the follow-up study. The acute onset of infarction in patients was used as the start date for each patient, and the development of the PBA was considered as the endpoint. The primary outcome variable was the presence or absence of PBA. A neurologist administered a brief questionnaire to both patients and their relatives to establish the diagnosis of PBA according to Kim's criteria.[15] PBA was diagnosed if the patients exhibited excessive or inappropriate laughing, crying, or both compared with their premorbid state. If both the patient and relative(s) who lived with the patient agreed that excessive or inappropriate laughing or crying occurred on two or more occasions beginning from the follow-up, the diagnosis of PBA was established. Follow-up assessments were performed by physicians who were blinded to the patient's hospital course. During a median follow-up period, we identified 26 incident cases of newly diagnosed PBA. Then, we randomly selected controls among the patients with post-infarction cognitive impairment who remained free from PBA and matched them to the case patients in a 1:1 ratio, according to age (within 2 year), sex,

and education background. The final study cohort consisted of 52 patients (Figure 1).

Neuropsychological assessment

Other than the MoCA, neuropsychological tests were grouped into 4 cognitive domains: 1) attention – the mainland Chinese version of the digit span test (DST) of the Wechsler Adult Intelligence Scale (WAIS-Rc) was used;[16] 2) memory – Auditory Verbal Learning Test–HuaShan version test (AVLT-H) was used to assess memory of the patients;[17] 3) executive functions – controllability and response inhibition of the patients was determined using part C of the short form of the Stroop test (24 items with 4 colors, StroopC test),[18] and the mental flexibility of the patients was measured by the verbal fluency tests (VFTs) (using the animal fluency test);[19] and 4) the visuospatial construction ability of the patients was evaluated by the executive clock-drawing task (CDT) developed by Royall.[20]

Radiological examination

An MRI, including DWI and sequence of proton density, was performed on each patient with a 1.5-T system (Sonata; Siemens Medical, Erlangen, Germany) within 7 days of admission. A neurologist and a radiologist, who were blind to the psychiatric diagnoses, assessed the MRIs. The MRI assessment included the following: 1) brain infarcts: the presence of acute infarcts affecting the frontal, temporal,
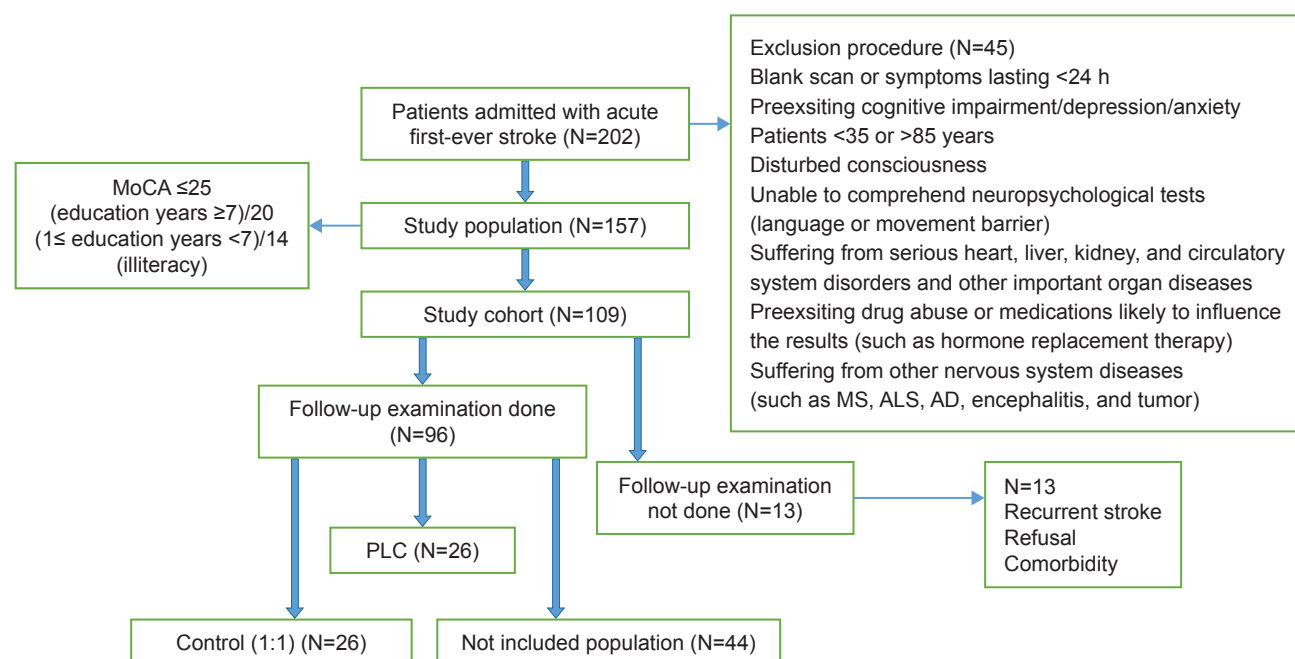

Figure 1 Flowchart of patient inclusion.
Abbreviations: PLC, pathological laughing and crying; MoCA, Montreal cognitive assessment; ALS, amyotrophic lateral sclerosis.

parietal, and occipital lobes; basal ganglia; thalamus; brainstem; cerebellar and subcortical white matter region; 2) white matter lesions: the extent of white matter lesions was graded using Fazekas' 4-point scale.[21] Periventricular lesions and deep white matter lesions were scored on proton density images.

Statistical analysis

Descriptive statistics are presented as frequencies, means, and standard deviation (SD). Differences between groups were examined with Fisher's exact test for proportions and with Student's t-test for continuous variables. In these analyses, the case and control subjects were matched by age, education years and sex within each center (1:1 pair matching). The associations between cognitive impairment in acute phase stroke and long-term PBA symptoms were investigated by conditional logistic regression analyses. In the first step, multivariate models were adjusted by white matter lesions, hypertension, diabetes, hyperlipidemia, smoking, drinking, and National Institute of Health Stroke Scale (NIHSS) total score. In the second step, we examined different cognitive domains at baseline

in multivariable regression models. All analyses were performed with SPSS statistical software version 13.0 (SPSS Inc, Chicago, IL, USA) and SAS statistical software version 9.2 (SAS Institute Inc, Carey, NC, USA). A P-value < 0.05 was accepted as indicating statistical significance.

Results

After the early phase of stroke, 26 (27.1%) patients demonstrated PBA during follow-up. Table 1 shows univariate associations between potential predictor variables and long-term PBA. PBA was independently associated with low MoCA scores in the acute stage of stroke. There were no significant differences between the two groups with respect to age, sex, years of education, smoking, drinking, hypertension, diabetes, hyperlipidemia, NIHSS total scores, and the extent of white matter lesions. The PBA group had significantly more acute infarcts in the frontal lobe and basal ganglia. Table 2 summarizes the results of multiple stepwise logistic regression analysis. Multivariable regression models adjusting for age, sex, years of education, smoking, drinking, lesion location, NIHSS total score, the extent

Table 1 Predictors of long-term PBA: characteristics of the study subjects at baseline

	Cases (N=26)					Controls (N=26)					P-value
	N	Mean	SD	N	%	N	Mean	SD	N	%	
Age (years)	26	62.27	7.54			26	61.46	7.46			
Gender (male/female)	26			12/14	46.15	26			12/14	46.15	
Years of education	26	7.30	2.80			26	7.40	2.80			
White matter lesions	26					26					
		0.96	0.59				0.88	0.70			0.658[a]
		1.19	0.73				1.07	0.73			0.556[a]
Localization of acute infarct	26					26					
Frontal lobe				10	38.46				4	15.38	0.1164[b]
Basal ganglia region				9	34.62				5	19.23	0.3487[b]
Frontal lobe and basal ganglia region				7	26.92				1	3.85	0.0496[b]
Temporal lobe				4	15.38				6	23.08	0.3497[b]
Parietal lobe				3	11.54				4	15.38	1.000[b]
Occipital lobe				1	3.85				4	15.38	1.000[b]
Brainstem				5	19.23				2	7.69	0.4189[b]
Cerebellar				2	7.69				2	7.69	1.000[b]
Thalamus				3	11.54				3	11.54	1.000[b]
Subcortical white matter				7	26.92				6	23.08	1.000[b]
More than one location				11	42.31				6	23.08	0.2367[b]
Smoking	26			15	57.70	26			12	46.15	0.5793[b]
Drinking	26			3	11.54	26			4	15.38	1.000[b]
Hypertension	26			20	76.92	26			17	65.38	0.5414[b]
Diabetes	26			12	46.15	26			10	38.46	0.7793[b]
Hyperlipidemia	26			21	80.77	26			19	73.08	0.7432[b]
NIHSS	26	5.19	2.84			26	4.73	2.59			0.545[a]
MMSE	26	19.81	3.20			26	21.88	2.34			0.010[a]
MoCA	26	16.60	4.80			26	19.70	3.30			0.001[a]

Notes: [a]Student's t-test for continuous variables. [b]Fisher's exact test for proportions. Variables shown as mean ± SD or frequencies.
Abbreviations: PBA, pseudobulbar affect; SD, standard deviation; NIHSS, National Institute of Health Stroke Scale; MMSE, minimum-mental state examination; MoCA, Montreal cognitive assessment.

Table 2 Predictors of long-term PBA: conditional logistic regression analysis

Variable	PBA at follow-up		
	OR	95% CI	*P*-value
MoCA	0.715	0.541–0.945	0.018
MMSE	0.461	0.241–0.882	0.019

Notes: Values are OR and 95% CI. Adjusted for smoking, drinking, diabetes, hypertension, hyperlipidemia, NIHSS scores, white matter lesion, and lesion location.
Abbreviations: PBA, pseudobulbar affect; OR, odds ratio; CI, confidence interval; MoCA, Montreal cognitive assessment; MMSE, minimum-mental state examination; NIHSS, National Institute of Health Stroke Scale.

Table 4 Multivariate adjusted ORs of PBA for cognitive domains

Variable	PBA at follow-up		
	OR	95% CI	*P*-value
Delayed recall (3 min)	0.641	0.401–1.024	0.0631
DST	0.386	0.163–0.911	0.030
StroopC-time	1.148	1.009–1.308	0.037
VFT	0.827	0.676–1.013	0.067
CDT	0.616	0.420–0.904	0.013

Notes: Values are OR and 95% CI. Adjusted for smoking, drinking, diabetes, hypertension, hyperlipidemia, NIHSS, white matter lesion, and lesion location.
Abbreviations: PBA, pseudobulbar affect; OR, odds ratio; CI, confidence interval; DST, digit span test; VFT, verbal fluency test; CDT, clock-drawing task.

of white matter lesion, and vascular risk factors showed that post-infarction low MoCA scores remained independent predictors of long-term PBA (odds ratio [OR]=0.72; 95% confidence interval [CI]=0.54–0.95; *P*=0.018).

Next, we examined which specific cognitive disorders at baseline were associated with PBA after the follow-up period (Table 3). Univariate logistic regression analysis showed that the PBA group had a significantly lower DST score, required more time to complete the StroopC test, and made more omission and errors in the CDT. There was no significant difference between groups in terms of memory as measured by the AVLT-H tests. Table 4 presents the results from multivariable regression models. After adjustment for age, sex, years of education, smoking, drinking, lesion location, NIHSS total score, the extent of white matter lesion and vascular risk factors, DST scores, StroopC time, and CDT scores remained significantly associated with PBA, respectively (OR=0.39, 95% CI=0.16–0.91, *P*=0.030; OR=1.15, 95% CI=1.01–1.31, *P*=0.037; OR=0.62, 95% CI=0.42–0.90, *P*=0.013).

Discussion

In this study, the incidence of cognitive impairment during the acute phase of first cerebral infarction was as high

Table 3 Predictors of long-term PBA: cognitive domain characteristics of the study subjects at baseline

Study variable	Cases (N=26)		Controls (N=26)		*P*-value
	Mean	SD	Mean	SD	
Delayed recall (3 min)	4.07	1.87	4.46	1.42	0.4011
Delayed recall (30 min)	3.42	1.92	4.19	1.39	0.1039
Recognition	6.92	2.80	7.31	2.34	0.5889
StroopC-time	50.38	18.57	40.73	12.41	0.0322
StroopC-error	3.50	3.30	2.08	2.26	0.0763
VFT	10.54	4.17	12.35	3.76	0.1065
DST	4.07	0.97	4.73	1.15	0.0329
CDT	6.69	2.69	8.38	2.90	0.0341

Abbreviations: PBA, pseudobulbar affect; SD, standard deviation; VFT, verbal fluency test; DST, digit span test; CDT, clock-drawing task.

as 69%. Likewise, the incidence of long-term PBA in the group with post-infarction cognitive impairment was up to 27%. Previous reports have shown that antidepressants used to treat PBA can improve cognitive function in patients after stroke,[22,23] which may indicate their correlation between PBA and cognitive impairment from one aspect. However, most studies on cognitive impairment in patients after infarction have focused on the long-term follow-up outcomes but rarely studied the effect of cognitive impairment during the acute phase on long-term PBA.

This study showed that the decline in cognitive function during the acute phase after cerebral infarction was an independent predictor of the development of long-term PBA. In addition, development of long-term PBA was associated with the severity of cognitive impairment. A previous study in ALS has shown that patients with PBA are more likely to have cognitive impairment.[24] Comparison of PBA cases after stroke with controls also shows that mild cognitive impairment is an independent risk factor for PBA.[11] These results were consistent with our findings. A possible explanation for these findings is that ischemic necrosis of the affected tissue in patients with acute cerebral infarction has damages to the neurological circuits of anatomical structures associated with cognitive function,[25] these loops, such as prefrontal lobe–basal ganglia loop, cerebral cortical–subcortical, and limbic system–diencephalon, intersect with the neural network of cortical–pontine–cerebellum loop, which is responsible for PBA.[26] Therefore, cognitive impairment is often accompanied by frontal lobe-related information output barrier, leading to disorders of gate-control for motor expression of emotion which can manifest as PBA.[26] Because PBA occurs in a wide variety of neurological disorders, specificity in the location of brain lesions appear to be more important to the pathogenesis of PBA. In our study, PBA and control groups had significant differences in frontal and basal ganglia infarcts.

Previous studies have shown that the site and severity of cerebral infarction, hypertension, diabetes, and lifestyles are risk factors associated with cognitive impairment in the patients with cerebral infarction.[27–32] However, this study suggested that although the above risk factors increased the risk of cerebral infarction-induced cognitive impairment, they were not closely related to the development of long-term PBA, which are unlikely to be useful as predictors of PBA.

We conducted neuropsychological tests to demonstrate a general loss of cognitive function during the acute phase of cerebral infarction. In addition, we further analyzed which specific cognitive domain was independently associated with the development of long-term PBA. We found that patients with visuospatial deficit, executive dysfunction, and attention deficit during the acute phase of stroke had relatively high incidence of long-term PBA after cerebral infarction. The comprehensive neuropsychological evaluation battery we conducted contains DST and StroopC test for attention and executive function. The CDT reflected not only the visuospatial function but also the executive function of patients with regards to numerical order integration and visuospatial organization (ie, frontal lobe function). The prefrontal region is closely associated with attention and executive function, and it is also involved in the processing of visuospatial memory.[33] Therefore, lower function in these three specific cognitive domains suggests that long-term PBA after acute infarction is associated with damage to the loop related to the frontal lobe, such as frontal–basal ganglia–pontine–cerebellar loop.[26] Studies of brain lesion location have suggested a wide-dispersed neural network involving frontal lobe in the pathophysiology of PBA. A recent study has supported this opinion that the prefrontal cortex is closely associated with PBA.[34]

Aharon-Peretz et al showed that despite the absence of clinically significant new vascular events, cognitive impairment is more and more serious with time prolonging after acute phase of infarction.[35] This is consistent with the findings of Metter et al,[36] who reported varying degrees of deficits in executive functioning and visuospatial construction ability after acute cerebral infarction. These may be due to the following: 1) subcortical lesions of related anatomical structures, resulting in secondary chronic cortical hypoperfusion and metabolic abnormalities;[36,37] 2) exacerbated latent small vessel disease in patients, such as the emergence of leukodystrophy or clinically silent new cerebral infarction; and 3) particularly evident aging-induced hemodynamic disorder in the prefrontal cortex, which is closely related to cognitive impairment.[38] The development of long-term PBA after acute phase of infarction and the development of long-term cognitive impairment may share the same potential mechanism.

In summary, this study showed that cognitive impairment during the acute phase after cerebral infarction was an independent risk factor for long-term PBA. Development of PBA was closely associated with executive function, attention, and visuospatial disorder. Frontal lobe involvement of the infarct appears to play an important role.

The primary limitation of this study is its relatively small sample size, which reduced the statistical power in determining the difference between groups in certain tests and the correlation between the severity of PBA and the specific cognitive disorders. It also resulted in a low power in detecting the potential differences between groups in terms of frontal lobe infarcts and basal ganglia infarcts. Furthermore, the assessment of post-infarction cognitive impairment was made only once. As patients who had had recurrent infarction before the 6-month follow-up were not included in the study, the sample was biased to an unknown degree.

Conclusion
Cognitive impairment in the first weeks after cerebral infarction is an important risk factor for long-term PBA symptoms. Future studies are warranted to examine the relation between symptoms of PBA and cognitive impairment in more detail.

Acknowledgments

Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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