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ORIGINAL RESEARCH

A Retrospective Study of Brain-Heart Syndrome in Patients with Acute Cerebrovascular Diseases

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Objective: To investigate the clinical characteristics, risk factors and outcomes of brain-heart syndrome (BHS) in patients with acute cerebrovascular diseases (ACVDs).

Methods: A retrospective analysis was conducted of 100 patients who were admitted to our hospital with ACVDs between January 2023 and December 2023. The demographic, clinical, laboratory and imaging data of the patients were collected, and the presence and severity of BHS were evaluated. The neurological and cardiac outcomes of the patients at discharge and at 12-month follow-up were also assessed.

Results: Out of the 100 patients, 38% had BHS, classified as mild (18%), moderate (12%) and severe (8%). The most prevalent ACVDs were cerebral infarction (58%), cerebral haemorrhage (32%) and subarachnoid haemorrhage (10%). Cardiac complications included arrhythmia (26%), myocardial ischaemia (18%) and heart failure (10%). Patients with BHS had higher results for blood pressure, heart rate, white blood cell count, C-reactive protein, IL-6, D-dimer and troponin, more severe neurological deficits, higher mortality and poorer functional outcomes. Multivariable analysis identified age, hypertension, diabetes, coronary artery disease, prior cardiovascular events, cerebral haemorrhage, brainstem infarction and hypothalamic or insular lesions as independent risk factors for BHS.

Conclusion: Brain-heart syndrome is a frequent, severe complication in patients with ACVD, linked with multiple risk factors and poor prognosis. Prompt diagnosis and treatment are crucial for improving patient outcomes.

Keywords: brain-heart syndrome, acute cerebrovascular diseases, cerebral infarction, cerebral haemorrhage

Introduction

Acute cerebrovascular diseases (ACVDs) are a group of disorders that affect the blood supply to the brain, resulting in ischaemic or haemorrhagic stroke.[1] They are a major cause of death and disability worldwide and place a heavy burden on both the health care system and society. According to the Global Burden of Disease Study 2019, ACVDs account for 10.4% of all deaths and 8.7% of all disability-adjusted life years globally.[2]

Acute cerebrovascular diseases can also cause various cardiac complications, such as myocardial ischaemia, myocardial injury, arrhythmia or heart failure. These complications are collectively referred to as brain-heart syndrome (BHS), which was first described as a reflex response to increased intracranial pressure by Cushing in 1945.[3] However, the concept of BHS has been expanded to include any cardiac dysfunction caused by ACVDs, regardless of the type, location or severity of the brain lesion.[4] Brain-heart syndrome can occur in up to 40% of patients with ACVDs and is associated with increased morbidity and mortality.[5]

The pathophysiology of BHS is complex and multifactorial, involving multiple mechanisms, such as neurogenic, humoral, inflammatory and iatrogenic factors.[6] The neurogenic mechanism is based on the disruption of the autonomic nervous system, which regulates cardiovascular function.[7] The brain lesions can affect the central or peripheral

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components of the autonomic nervous system, leading to sympathetic overactivation, parasympathetic withdrawal or both.[8] The sympathetic overactivation can cause catecholamine release, which can induce myocardial ischaemia, injury or necrosis, as well as arrhythmia and heart failure.[9] The parasympathetic withdrawal can cause tachycardia, atrial fibrillation (AF) or ventricular arrhythmia.[10] The humoral mechanism is based on the release of various biomarkers, such as natriuretic peptides, troponins, cytokines and chemokines, which can reflect the cardiac stress, injury or inflammation caused by ACVDs.[11] The inflammatory mechanism is based on the activation of the innate and adaptive immune system, which can trigger a systemic inflammatory response syndrome or a cytokine storm, leading to multiple organ dysfunction syndrome or acute respiratory distress syndrome.[12] The iatrogenic mechanism is based on the adverse effects of the drugs or interventions used to treat ACVDs, such as anticoagulants, antiplatelets, thrombolytics or mechanical thrombectomy, which can increase the risk of bleeding, infection or embolism.[13,14]

The diagnosis and treatment of BHS are challenging and require a multidisciplinary approach. The diagnosis of BHS is based on the clinical presentation, electrocardiography (ECG), echocardiography, cardiac biomarkers and brain imaging.[15] The treatment of BHS is based on the type and severity of the cardiac complication, the type and location of the brain lesion, and the balance between the benefits and risks of the therapeutic options.[16] The treatment of BHS may include pharmacological agents, such as beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, nitrates, antiarrhythmics, anticoagulants or antiplatelets, as well as non-pharmacological interventions, such as cardiac pacing, defibrillation, cardioversion or implantable cardioverter-defibrillator.[17,18] The treatment of BHS should also consider the prevention and management of potential complications, such as hypotension, hypertension, hypoxia, hyperglycaemia or electrolyte imbalance.[19]

The aim of this study is to investigate the clinical characteristics, risk factors and outcomes of BHS in patients with ACVDs. A retrospective analysis was conducted of 100 patients who were admitted to our hospital with ACVDs between January 2023 and December 2023, to assess the neurological and cardiac outcomes of the patients at discharge and at 3-month follow-up. It is hoped that the findings can provide insights into the epidemiology, pathophysiology, diagnosis and treatment of BHS and can contribute to the improvement of the quality of care and the prognosis of patients with ACVDs.

Methods

Study Design and Population

The study was conducted at a tertiary care hospital equipped with comprehensive neurological and cardiological facilities. A retrospective cohort study was conducted of 100 consecutive patients who were admitted to the Department of Neurology of our hospital with a diagnosis of ACVD between January 2023 and December 2023. The inclusion criteria were: (1) age ≥ 18 years; (2) confirmed diagnosis of ACVD by clinical symptoms, signs and brain imaging; and (3) availability of complete medical records, including demographic, clinical, laboratory and imaging data. The exclusion criteria were: (1) history of cardiac diseases, such as myocardial infarction, angina, heart failure, arrhythmia or valvular diseases; (2) history of cardiac surgery or intervention, such as coronary artery bypass grafting, percutaneous coronary intervention or valve replacement; (3) history of chronic kidney disease (CKD), liver disease or malignancy; and (4) refusal to participate or lack of informed consent. The study protocol was approved by the ethics committee of the hospital, and informed consent was obtained from the patients or their legal representatives. A 30-day window was used to define cardiovascular complications directly related to the neurological event. All patients were followed up for at least 30 days from admission to ensure capture of all potential BHS events.

Data Collection and Definition

The following data was collected from the electronic medical records of the patients: (1) demographic data, such as age, sex and body mass index; (2) clinical data, such as medical history, risk factors, vital signs, neurological examination and Glasgow Coma Scale (GCS); (3) laboratory data, such as blood cell count, liver function, renal function, glucose, lipids, electrolytes, lactate, and coagulation, inflammation and cardiac biomarkers; and (4) imaging data, such as brain computed tomography, magnetic resonance imaging, angiography and echocardiography. The type, location and size of the brain lesion were recorded, as well as the type and severity of the cardiac complication, the treatment modalities and any

complications during hospitalisation. Data was also collected on additional cardiovascular risk factors: dyslipidemia, CKD, chronic obstructive pulmonary disease, peripheral artery disease and AF.

The diagnosis of ACVD was based on the clinical symptoms, signs and brain imaging findings, according to the World Health Organization criteria.[20] The type of ACVD was classified as cerebral haemorrhage, cerebral infarction or subarachnoid haemorrhage, according to the location and nature of the brain lesion. The diagnosis of BHS was based on the presence of any cardiac complication caused by ACVDs, according to the criteria of Mayo Clinic.[21] The severity of BHS was graded as follows: (1) mild BHS: minor cardiac abnormalities without haemodynamic instability or organ dysfunction, which included transient arrhythmias or mild troponin elevation (1–2 times the upper limit of normal) not requiring specific treatment; (2) moderate BHS: significant cardiac abnormalities requiring medical intervention but not life-threatening, which included persistent arrhythmias, moderate troponin elevation (2–5 times the upper limit of normal) or mild heart failure (ejection fraction 40–49%) requiring medication but not intensive care; and (3) severe BHS: life-threatening cardiac complications requiring intensive care or urgent intervention, which included malignant arrhythmias, acute myocardial infarction, severe heart failure (ejection fraction <40%) or cardiogenic shock, requiring vasoactive drug support or mechanical assist devices. The cardiac complications were defined as follows: (1) myocardial ischaemia: new or worsening chest pain with ST-segment depression or elevation, or T-wave inversion on ECG, or new regional wall motion abnormality on echocardiography; isolated chest pain was not considered myocardial ischaemia; (2) myocardial injury: elevation of troponin level above the 99th percentile of the upper reference limit, with or without ECG or echocardiographic changes; even minor elevations were considered, and any elevation above the upper reference limit was recorded; (3) arrhythmia: new-onset or worsening of AF, atrial flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation or heart block, where "worsening" refers to increased frequency or duration; and (4) heart failure: new or worsening signs and symptoms of pulmonary or systemic congestion, reduced left ventricular ejection fraction (<50%) or increased left ventricular end-diastolic diameter (>56 mm) on echocardiography. The severity of BHS was graded as mild, moderate or severe, according to the impact of the cardiac complication on the haemodynamic stability, organ perfusion and clinical outcome of the patient.

The neurological outcome was assessed by the modified Rankin Scale (mRS) at discharge and at 3-month follow-up.[22] The mRS is a 7-point scale that measures the degree of disability or dependence in daily activities, ranging from 0 (no symptoms) to 6 (death). The cardiac outcome was assessed by the occurrence of major adverse cardiac events (MACE) at discharge and at 12-month follow-up; the MACE were defined as cardiac death, nonfatal myocardial infarction or nonfatal stroke.

Statistical Analysis

The statistical analysis was performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarise the data, such as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. The chi-square test or Fisher's exact test were used for categorical variables, and the *t*-test or Mann–Whitney *U*-test were used for continuous variables, to compare the differences between the patients with and without BHS. The multivariable logistic regression analysis was used to identify the independent risk factors for BHS, and the odds ratio and 95% confidence interval (CI) were reported. The Kaplan-Meier method and the Log rank test were used to compare the survival curves of the patients with and without BHS. The Cox proportional hazards model was used to estimate the hazard ratio and 95% CI for the association between BHS and MACE. A P-value of less than 0.05 was considered as statistically significant.

Results

Baseline Characteristics

The baseline characteristics of the 100 patients with ACVD are shown in Table 1. The mean age of the patients was 68.4 ± 12.3 years, and 54 (54%) were men. The most common risk factors were hypertension (72%), Dyslipidemia (45%), diabetes (32%) and smoking (28%). The most common types of ACVD were cerebral infarction (58%), followed by cerebral haemorrhage (32%) and subarachnoid haemorrhage (10%). The mean GCS score at admission was 13.2 ± 3.1, and the mean mRS score at discharge was 3.6 ± 1.8. The median length of hospital stay was 14 days (interquartile range: 10–21 days). Patients with BHS had significantly longer hospital stays than those without BHS (median: 18 days vs 12 days, P < 0.01).

Table 1 Baseline Characteristics of the Patients with ACVDs

Variable	Total (n = 100)	BHS (n = 38)	No BHS (n = 62)	P value
Age (years)	68.4 ± 12.3	72.1 ± 11.2	66.1 ± 12.7	0.02
Sex (male)	54 (54%)	22 (57.9%)	32 (51.6%)	0.54
BMI (kg/m^2)	24.5 ± 3.6	24.8 ± 3.9	24.3 ± 3.4	0.46
Hypertension	72 (72%)	32 (84.2%)	40 (64.5%)	0.04
Diabetes	32 (32%)	16 (42.1%)	16 (25.8%)	0.11
Smoking	28 (28%)	12 (31.6%)	16 (25.8%)	0.56
Dyslipidemia	45 (45%)	20 (52.6%)	25 (40.3%)	0.23
Chronic kidney disease	18 (18%)	9 (23.7%)	9 (14.5%)	0.25
COPD	12 (12%)	6 (15.8%)	6 (9.7%)	0.37
Peripheral artery disease	8 (8%)	4 (10.5%)	4 (6.5%)	0.47
Atrial fibrillation	22 (22%)	11 (28.9%)	11 (17.7%)	0.19
GCS score at admission	13.2 ± 3.1	12.4 ± 3.4	13.7 ± 2.9	0.03
mRS score at discharge	3.6 ± 1.8	4.3 ± 1.6	3.2 ± 1.7	<0.01
Hospital stay (days)	14	18	12	<0.01

Abbreviations: ACVDs, acute cerebrovascular diseases; BMI, Body mass index; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale.

Brain-Heart Syndrome Characteristics and Outcomes

The characteristics and outcomes of the 38 patients with BHS are shown in Table 2. The most common type of cardiac complication was arrhythmia (26%), followed by myocardial ischaemia (18%), myocardial injury (16%) and heart failure (10%). The severity of BHS was mild in 18 (47.4%%) patients, moderate in 12 (31.6%) patients and severe in 8 (21.1%) patients. The patients with BHS had higher blood pressure, heart rate, white blood cell (WBC) count, C-reactive protein, interleukin-6, D-dimer and troponin levels than those without BHS (all $P < 0.05$). The patients with BHS also had more severe neurological deficits, higher mortality and worse functional outcomes than those without BHS (all $P < 0.05$).

Table 2 BHS Characteristics and Outcomes

Variable	BHS (n = 38)	No BHS (n = 62)	P value
Type of cardiac complication			
• Myocardial ischemia	7 (18.4%)	0 (0%)	<0.01
• Myocardial injury	6 (15.8%)	0 (0%)	<0.01
• Arrhythmia	10 (26.3%)	0 (0%)	<0.01
• Heart failure	4 (10.5%)	0 (0%)	0.02
Severity of BHS			
• Mild	18 (47.4%)		
• Moderate	12 (31.6%)		
• Severe	8 (21.1%)		
BP (mmHg)	158/92 ± 18/12	142/84 ± 16/10	<0.01
HR (bpm)	98 ± 15	82 ± 12	<0.01
WBC (×10^9/L)	9.8 ± 3.2	7.6 ± 2.4	<0.01
CRP (mg/L)	18.4 ± 12.6	8.2 ± 6.4	<0.01
IL-6 (pg/mL)	32.6 ± 18.4	12.4 ± 8.6	<0.01
D-dimer (mg/L)	3.7 ± 2.1	1.5 ± 0.9	<0.01
Troponin (ng/mL)	0.12 ± 0.08	0.02 ± 0.01	<0.01
Neurological outcome			
• mRS score at 3-month follow-up	4.6 ± 1.7	2.8 ± 1.6	<0.01
• Death	12 (31.6%)	6 (9.7%)	0.01
Cardiac outcome			
• MACE	16 (42.1%)	8 (12.9%)	<0.01
• Death	8 (21.1%)	2 (3.2%)	0.01

Abbreviations: BHS, brain-heart syndrome; BP, Blood pressure; HR, heart rate; WBC, white blood cell; CRP, C-reactive protein; MACE, major adverse cardiac events.

Table 3 Multivariate Logistic Regression Analysis of the Risk Factors for BHS

Variable	Odds Ratio	95% Confidence Interval	P value
Age	1.05	1.01–1.09	0.02
Hypertension	2.74	1.12–6.71	0.03
Diabetes	2.13	0.87–5.22	0.09
Coronary artery disease	3.21	1.28–8.04	0.01
Cerebral hemorrhage	3.17	1.25–8.03	0.01
Brainstem infarction	4.32	1.72–10.84	<0.01
Brain lesions involving the hypothalamus or the insula	3.56	1.41–8.98	0.01

Abbreviation: BHS, brain-heart syndrome.

Multivariable Logistic Regression Analysis for BHS

The multivariable logistic regression analysis showed that age, hypertension, diabetes, coronary artery disease, cerebral haemorrhage, brainstem infarction and brain lesions involving the hypothalamus or the insula were independent risk factors for BHS (Table 3).

Effect of Brain-Heart Syndrome on Major Adverse Cardiac Events and Survival Rate

Multivariable Cox proportional hazards regression analysis showed that BHS was an independent predictor of MACE (hazard ratio: 2.74, 95% CI: 1.32–5.68, P = 0.01). After adjusting for age and sex, BHS remained an independent predictor of MACE (adjusted hazard ratio: 2.31, 95% CI: 1.12–4.76, P = 0.023). The Kaplan-Meier survival analysis showed that the patients with BHS had a lower survival rate than those without BHS (Log rank test, P < 0.01) (Figure 1).

Discussion

In this study, the clinical characteristics, risk factors and outcomes of BHS in 100 patients with ACVDs were retrospectively analysed. Brian-heart syndrome was found to be a common and serious complication of ACVDs, affecting 38% of the patients. The patients with BHS had more severe neurological deficits, higher mortality and worse functional outcomes than those without BHS. Several risk factors for BHS were also identified, such as age, hypertension, diabetes,

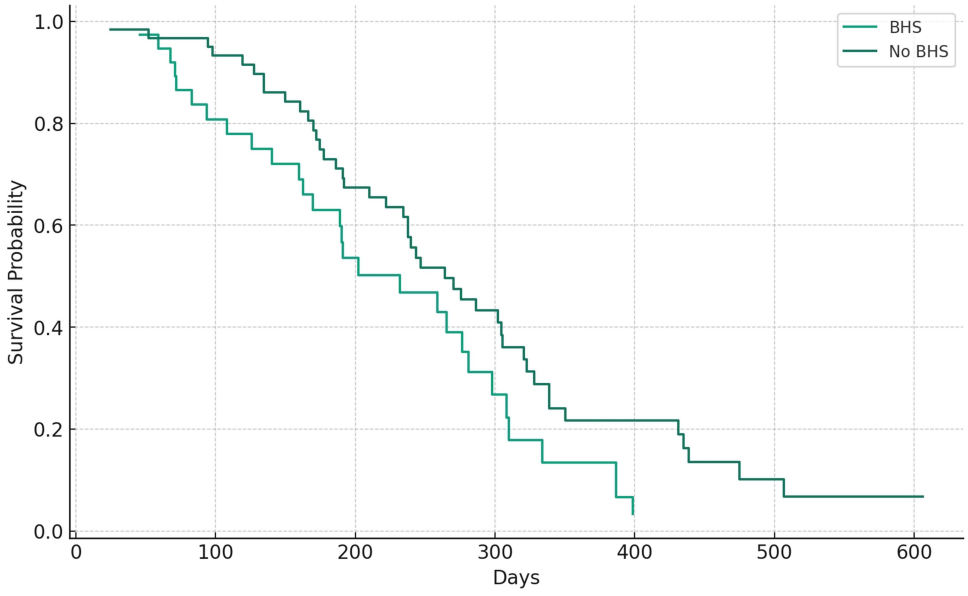

Figure 1 Kaplan-Meier survival curves of the patients with and without BHS.

coronary artery disease, cerebral haemorrhage, brainstem infarction and brain lesions involving the hypothalamus or the insula.

The findings of this study are consistent with previous studies that reported high prevalence and poor prognosis of BHS in patients with ACVDs. For example, a study involving patients with ACVDs found that BHS was associated with increased risk of death, disability and recurrence of stroke.[23] Another study found that BHS was associated with increased risk of cardiac events, neurological deterioration and poor quality of life in patients with ACVDs.[24]

Age is a well-known risk factor for both ACVDs and BHS, as ageing is associated with increased vascular stiffness, endothelial dysfunction, oxidative stress and inflammation, which can impair cerebral and cardiac perfusion and function.[25] Hypertension and diabetes are also common risk factors for both ACVDs and BHS, as they can cause damage to the cerebral and cardiac vessels or cause metabolic disturbances and oxidative stress-related endothelial dysfunction, which can affect cerebral and cardiac metabolism and function.[26] Inflammatory processes play a pivotal role in the pathophysiology of both acute neurological events and subsequent cardiovascular complications. In this study, levels of inflammatory markers, including WBC count, C-reactive protein, IL-6 and D-dimer, were significantly elevated in patients experiencing BHS compared with those with early cardiovascular complications following ACVDs. These findings underscore the potential role of inflammation in mediating adverse cardiovascular outcomes in this patient population. Previous studies have highlighted the association between systemic inflammation and cardiovascular events in various clinical contexts, including stroke.[27,28]

This study also revealed novel risk factors for BHS, such as lesions involving the cerebrum, brainstem, hypothalamus and insula. Cerebral haemorrhage and brainstem infarction can cause increased intracranial pressure, brain herniation or direct damage to the brainstem, which can affect the autonomic nervous system and cardiovascular regulation.[29,30] In addition, the hypothalamus and the insula are important regions of the brain that regulate the autonomic nervous system and cardiovascular function.[8] The hypothalamus controls sympathetic and parasympathetic tone, blood pressure, heart rate and body temperature.[31] The insula integrates sensory, emotional and cognitive information, and modulates cardiac output, vascular resistance and baroreflex sensitivity.[32] Damage to these regions can disrupt the balance of the autonomic nervous system and cause sympathetic overactivation, parasympathetic withdrawal or both, leading to BHS. Previous studies have shown that patients with ACVDs involving the hypothalamus or the insula had higher incidence and severity of BHS than those without.[10,32]

The diagnosis and treatment of BHS are challenging and require a multidisciplinary approach. However, some of methods used for BHS diagnosis may have limitations or drawbacks, such as low sensitivity, high cost or invasiveness.[15] The options for BHS treatments, such as anticoagulants, antiplatelets or beta-blockers, may have conflicting or unknown effects, which may increase the risk of bleeding, worsen the neurological outcome or reduce cardiac output.[9] Therefore, novel biomarkers and algorithms may be the future direction to develop more reliable and convenient methods for BHS diagnosis. There is also a need for more evidence-based and individualised guidelines for the diagnosis and treatment of BHS.

This study has some limitations that should be acknowledged. First, it was a retrospective analysis of a single-center cohort, which may limit the generalisability and validity of the results. Second, a relatively small sample size and a short follow-up period were used, which may affect the statistical power and reliability of the results. Third, potential confounders or modifiers, such as genetic factors, environmental factors or medication adherence, were not considered in this study, all of which may influence the occurrence and outcome of BHS. Fourth, no subgroup analysis or stratified analysis was performed according to the type or the severity of BHS, which may obscure some important differences or associations. Fifth, a standardised or validated diagnostic criteria or grading system for BHS were not used in this study, which may introduce bias or inconsistency in the results. Finally, while patients with known symptomatic cardiac disease were excluded, the possibility that some patients may have had asymptomatic cardiac conditions that were only detected during post-stroke cardiovascular assessment cannot be ruled out, and may have affected the assessment of BHS risk factors. Furthermore, the BHS severity grading criteria used, although based on clinical practice, have not been thoroughly validated, which may have influenced the assessment of BHS severity.

Conclusion

In conclusion, this study demonstrates that BHS is a common and serious complication of ACVDs, associated with poor prognosis. Further studies are needed to explore the pathophysiology, biomarkers and optimal treatment of BHS.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Xuanwu Hospital of China Capital Medical University.

Written informed consent was obtained from the patients or their legal representatives.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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