RESEARCH ARTICLE

Premature atrial contractions and their associations with cryptogenic strokes

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Abstract

Objective: To assess the association between premature atrial contractions and cryptogenic stroke while comparing the prevalence of premature atrial contractions among cryptogenic and non-cryptogenic stroke patients.

Method: The retrospective, cross-sectional study was conducted at the Shifa International Hospital, Islamabad, Pakistan, and comprised data from January 2020 to April 2021 of patients diagnosed with ischemic stroke on magnetic resonance imaging of the brain, and who underwent investigation and treatment according to the national stroke guidelines. Patients with cryptogenic stroke were placed in group A, and those with non-cryptogenic stroke in group B. Data on demographic information, stroke type, risk factors, and cardiac assessment was collected from the institutional electronic medical records. Data was analysed using SPSS 25.

Results: Of the 118 patients, 44(37.3%) were in group A; 35(79.5%) males and 9(20.5%) females with mean age 64.09±12.28 years. There were 74(62.7%) patients in group B; 57(77%) males and 17(23%) females with mean age 65.56±12.12 years. Premature atrial contractions were detected in 43(97.7%) group A patients compared to 1 patient (2.3%) in group B ($p<0.05$), and demonstrated significant association with atrial fibrillation, dyslipidaemia, mitral stenosis and left ventricular systolic dysfunction ($p<0.05$) in group A, and with atrial fibrillation, previous myocardial infarction, left atrium dilatation, wall akinesia, left carotid artery stenosis, and left ventricular systolic dysfunction in group B ($p<0.05$).

Conclusion: Prolonged cardiac monitoring pf stroke patients is critical to any effort to identify occult atrial fibrillation. Besides, premature atrial contractions were significantly associated with cardiac risk factors.

Key Words: Atrial fibrillation, Stroke, Cryptogenic, Premature atrial contractions, Holter monitoring.

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Introduction

Strokes remain a significant cause of morbidity and mortality worldwide, affecting over 13.7 million people annually.[1] Stroke incidence is disproportionately high in the Asian population, accounting for over two-thirds of all cases. Ischemic strokes, which account for approximately 9.5 million patients globally, can be classified as cryptogenic or non-cryptogenic. Cryptogenic strokes account for 15-40% of all ischemic strokes, and have recently become a significant public health concern.[2,3] Recent studies have demonstrated that cryptogenic strokes are particularly prevalent in individuals aged <45 years, with a prevalence of 55% compared to 42% in older individuals.[4] Therefore, there is an urgent need to focus on the prevention of cryptogenic strokes to reduce the impact of this condition, particularly in younger individuals.[5]

Atrial fibrillation (AF), a well-known cause of ischemic strokes, is often difficult to detect, even with prolonged rhythm monitoring. Moreover, identifying patients at risk of AF remains a significant challenge.[6] Therefore, early detection of AF is crucial in preventing ischemic strokes and reducing healthcare costs.[7]

Premature atrial contractions (PACs), triggered from the atrial myocardium, are more commonly detected on longer-duration Holter monitoring than on a normal electrocardiogram (ECG). They are generally considered clinically insignificant in the general population.[8] However, recent studies have revealed that PACs can be a marker of atrial myopathy and can significantly correlate with AF and ischemic strokes. Therefore, investigating the association involving PACs, cryptogenic strokes and other risk factors can help in the early detection of AF, and improve stroke prevention.[9-11]

The current study was planned to assess the association between PACs and cryptogenic stroke while comparing

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PAC prevalence among cryptogenic and non-cryptogenic stroke patients.

Materials and Methods

The retrospective, cross-sectional study was conducted at the Shifa International Hospital, Islamabad, Pakistan, and comprised data from January 2020 to April 2021 of patients diagnosed with ischemic stroke who underwent investigation and treatment according to the national stroke guidelines for the standard of care.[12]

After approval form the institutional ethics review committee, the sample size was calculated using G*Power with statistical power 80% and level of significance 0.05.[13] The sample was raised using convenience sampling technique. Those included were patients with ischemic stroke diagnosed on magnetic resonance imaging (MRI) of the brain, and who underwent 48-hour Holter monitoring, carotid Doppler, echocardiography, lipid profile, glycated haemoglobin (HbA1c), thrombotic profile, and immunological studies. Those excluded were patients aged <18 years, those who underwent incomplete workup, and those diagnosed with haemorrhagic strokes on MRI.

Data was extracted from the institutional electronic medical records using a standardised data-collection form. Data included baseline demographic information, stroke types, risk factors, carotid Doppler and transoesophageal echocardiography (TEE), as well as thrombotic profile and immunological analysis. Patients with cryptogenic stroke were placed in group A, and those with non-cryptogenic stroke in group B.

Data was analysed using SPSS 25. Continuous variables were expressed as means ± standard deviation for normally distributed data. Categorical variables were expressed as frequencies and percentages. Chi-square test was used to compare categorical variables. Logistic regression analysis was conducted with odds ratio (OR) and 95% confidence interval (CI). P<0.05 was considered statistically significant.

Results

Of the 118 patients, 44(37.3%) were in group A; 35(79.5%) males and 9(20.5%) females with mean age 64.09±12.28 years. There were 74 (62.7%) patients in group B; 57(77%) males and 17(23%) females with mean age 65.56±12.12 years. Hypertension (HTN), diabetes mellitus (DM), dyslipidaemia, and a history of ischemic stroke were common in both groups, and there was no significant difference between the groups (Table 1).

PACs were detected in 43(97.7%) group A patients compared to 62(83.8%) in group B (p<0.05). Patients with PACs demonstrated a significant association with AF (p=0.001), dyslipidaemia (p=0.016), mitral stenosis (p=0.015), and left ventricular systolic dysfunction (LVSD) (p=0.002).

Among non-cryptogenic cases, AF, previous myocardial infarction (MI), left atrium dilatation, wall akinesia, left carotid artery stenosis (LCAS), and LVSD were observed in 16(21.6%), 15(20.5%), 12(16.2%), 21(28.4%), [14](18.9%) and 34(45.9%) patients, respectively. Significant associations were observed for non-cryptogenic stroke with AF (p=0.002), previous MI (p=0.005), left atrium dilatation (p=0.019), wall akinesia (p=0.001), LCAS (p=0.004), and LVSD (p=0.002).

Overall, AF was seen in 16(21.6%) patients, and 10(62.5%) of them exhibited PACs. All the 49(100%) patients with atrial runs and 2(100%) with mitral stenosis showed PACs. Dyslipidaemia was noted in 13(11%) patients, and 9(69.2%) of them showed PACs (Table).

A significant association between PACs and an increased risk of cryptogenic stroke was seen (OR: 6.0; 95% CI: 1.5-24.0). Conversely, AF (OR: 0.3; 95% CI: 0.1-0.6), previous MI (OR: 0.2; 95% CI: 0.05-0.7), LVSD (OR: 0.4; 95% CI: 0.2-0.8), and LCAS (OR: 0.3; 95% CI: 0.1-0.8) were associated with a decreased likelihood of cryptogenic stroke.

Discussion

The current study demonstrated significant association between PACs and cryptogenic stroke, supporting the hypothesis that excessive PACs could be a marker or manifestation of an underlying atrial myopathy, thereby increasing the risk of stroke.[5] Consistent with previous studies, the current study demonstrated a significantly higher PAC burden in patients who subsequently develop AF and ischemic stroke. These studies have reported PACs as a poor prognostic factor associated with new-onset AF and recurrent strokes.[14,15] Furthermore, the current study observed a significant association between PACs and specific risk factors, such as dyslipidaemia, mitral stenosis and LVSD. These associations provide valuable insights into the pathophysiological basis of PACs.

Unlike previous studies, the current study observed no significant association between cryptogenic stroke patients and risk factors, such as HTN, DM, dyslipidaemia and history of ischemic stroke. Previous studies identified PACs as a valuable factor for detecting subclinical AF in cryptogenic stroke patients through cardiac monitoring.[11,16-18] Consistent with these findings, a Japanese cohort of 63,197 individuals without known cardiovascular disease reported significant associations between PACs and AF in men and women.[19] The current study confirmed these reports by demonstrating that patients with PACs were at a potential risk for hidden AF. Consequently, patients with unclear mechanisms of stroke with PACs are likely to benefit from prolonged cardiac monitoring.

The identification of patients with apparent AF who would benefit from early anticoagulation presents a significant clinical challenge. Previous studies that investigated the efficacy of direct oral anticoagulants (DOACs) compared to antiplatelet therapy in patients with cryptogenic stroke in the absence of AF yielded inconclusive results.[20] These studies failed to demonstrate the superiority of DOACs over antiplatelet therapy in preventing recurrent strokes. Furthermore, recent guidelines have not recommended the routine use of DOACs for primary prevention in such cases.[7] Therefore, it is crucial to identify any asymptomatic AF to determine the primary prevention of stroke in patients with PACs.

In addition, previous studies demonstrated a significantly high PAC burden associated with HTN, increasing age, and vascular risk factors.[6] The current study established a strong association of PACs with dyslipidaemia and other cardiac factors, such as LVSD, mitral stenosis, and atrial runs. These findings emphasise the multifactorial nature of PACs and their potential implications in the pathogenesis of cryptogenic strokes.

One important finding in the current study was the significant association between non-cryptogenic stroke and cardiac factors, such as left atrium dilatation, AF, previous MI, wall akinesia, LCAS, and LVSD. These cardiac factors can be a potential source of AF, leading to cardio-embolic strokes in these patients.

On the basis of current findings, it is not recommended that physicians initiate treatment solely based on the presence of frequent PACs, irrespective of whether AF has been detected. The management of patients with PACs should be guided by comprehensive clinical assessment, including the evaluation of individual risk factors, underlying cardiac conditions, and the presence of associated symptoms. To further improve patient outcomes, future prospective studies could explore the use of advanced cardiac imaging modalities and genetic markers to better understand the underlying pathophysiology of PACs and cryptogenic stroke. In addition, randomised controlled trials investigating the effectiveness of specific interventions, such as lifestyle modifications and targeted medications, in reducing stroke risk among patients with PACs and cryptogenic strokes could be warranted.

Table: Baseline characteristics and risk factors in cryptogenic and non-cryptogenic stroke patients.

Characteristics	Cryptogenic strokes n = 44	Non-cryptogenic strokes n = 74	P-values
Premature atrial contractions	43 (97.7%)	62 (83.8%)	0.019
PACs < 30/h	40 (90.9%)	57 (77%)	0.086
PACs > 30/h	3 (6.8%)	3 (4.1%)	0.098
Atrial fibrillation	Nil	16 (21.6%)	0.002
Atrial runs	13 (29.5%)	36 (35.1%)	0.532
Hypertension	17 (38.6%)	37 (50%)	0.231
Diabetes mellitus	29 (65.9%)	45 (60.8%)	0.580
Dyslipidaemia	5 (11.4%)	8 (10.8%)	0.926
Previous myocardial infarction	1 (2.3%)	15 (20.5%)	0.005
Previous ischemic stroke	10 (22.7%)	14 (18.9%)	0.619
Right carotid artery stenosis (> 50%)	Nil	8 (6.8%)	0.077
Left carotid artery stenosis (> 50%)	Nil	14 (18.9%)	0.004
Left atrium dilated	1 (2.3%)	12 (16.2%)	0.019
Mitral stenosis	Nil	2 (2.7%)	0.400
Left ventricular systolic dysfunction	4 (9.1%)	34 (45.9%)	0.002
Left ventricular apical thrombus	Nil	4 (5.4%)	0.117
Wall akinesia	Nil	21 (28.4%)	0.001

PAC: Premature atrial contraction.

The current study has several limitations. First, the lack of prolonged monitoring devices, such as implantable loop recorders, might have led to an underestimation of AF cases. Second, the relatively small sample size might have limited the generalisability of the results. Third, the retrospective study design might have introduced inherent biases and limitations in data collection and analysis. Finally, the timing of Holter monitoring following the stroke was based on routine institutional waiting periods, which may have resulted in neurologically-mediated cardiac remodelling and an increased occurrence of PACs. This observation raises the possibility of reverse causality, where stroke-related changes in the nervous system could have contributed to the development of PACs.

Despite the limitations, however, the current study is the first conducted at a centre with a well-established stroke unit in Pakistan, which could potentially offer a more comprehensive evaluation and management of patients with cryptogenic strokes compared to centres with more limited resources or expertise. Besides, the study found a higher number of cryptogenic stroke patients compared to previously reported studies.[7]

Conclusion

There was a significant association between PACs and cryptogenic stroke. Considering the significant association between PACs and AF, prolonged cardiac monitoring in cryptogenic stroke patients is recommended to uncover occult AF. This strategy may facilitate early intervention and prevention.

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AUTHORS' CONTRIBUTIONS:

MKK: Concept, design, data acquisition, collection, experiments, statistical analysis, drafting, revision, final approval and agreement to be accountable for all aspects of the work.

MF: Data acquisition, collection, experimental procedures, data analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.

RFS, WTM, LF & SS: Concept, design, data acquisition, analysis, drafting, revision, final approval and agreement to be accountable for all aspects of the work.