Transthoracic echocardiographic and clinical predictors in first versus recurrent ischemic strokes

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ABSTRACT

Recurrent strokes are more likely to be disabling or fatal than first ever strokes. The aim of the study is to evaluate transthoracic echocardiographic (TTE) and clinical predictors in patients with first versus those with recurrent ischemic strokes. A prospective observational comparative study of 217 patients admitted with ischemic strokes who were in sinus rhythm. Two groups of patients were simultaneously enrolled. The first group was 110 patients with first ischemic stroke and the second was 107 patients with recurrent ischemic stroke. TTE was done for all patients. Both echocardiographic and clinical risk factors were compared between both groups. Logistic regression analysis identified predictors for recurrent strokes. Among clinical risk factors hypertension, hyperlipidemia, family history of atherosclerotic vascular disease, prior coronary artery disease, peripheral vascular disease, and chronic kidney disease were significantly higher in recurrent stroke group. Multivariate logistic analysis identified age (OR, 1.03; 95% CI, 1.01 - 1.07), hypertension (OR, 2.25; 95% CI, 1.03 - 4.92), and hyperlipidemia (OR, 2.73; 95% CI, 1.40 - 5.35), as predictors for recurrent ischemic strokes. Left ventricular diastolic dysfunction, left ventricular hypertrophy (LVH) and aortic sclerosis were significantly more common in the recurrent stroke group compared to the first stroke group. However, in multivariate logistic analysis only LVH (OR, 3.50; 95% CI, 1.69 - 7.23), was identified as a predictor for recurrent strokes. Older age, hypertension, hyperlipidemia and left ventricular hypertrophy are significant predictors of recurrent ischemic strokes in patients with sinus rhythm. Those patients need more aggressive lipid lowering therapy and optimal blood pressure control.

KEYWORDS

Echocardiography; Risk Factors; Predictors;
Ischemic Stroke

1. INTRODUCTION

Recurrent strokes are more likely to be disabling or fatal than first ever strokes [1]. Identifying characteristics of people at high risk of recurrence has important implications for planning secondary prevention strategies to reduce the disease burden. However, despite all efforts to reduce the risk of recurrence, 25% of stroke patients are reported to suffer from recurrent stroke [2]. The most relevant predictors of stroke recurrence identified in epidemiological trials include advancing age, arterial hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia [3,4]. However trials focusing on echocardiographic predictors for stroke recurrence are limited.

The goal of this study was to identify clinical and transthoracic echocardiographic predictors by comparing patients with first ischemic strokes and those with recurrent ischemic strokes. We also aimed to examine if echocardiographic risk stratification would be of additional value in predicting the recurrence of strokes compared with clinical predictors alone.

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2. METHODS

We conducted a prospective observational comparative study of 217 patients admitted to Mubarak Al-Kabeer hospital in Kuwait from January 2011, to January 2013, with the diagnosis of acute ischemic stroke and who were in sinus rhythm. Two groups of patients were simultaneously enrolled. The first group included 110 patients with first ischemic stroke and the second group included 107 patients with recurrent documented ischemic stroke. Informed consent was obtained from all patients.

All patients admitted with stroke were screened for inclusion in the study. Patients were not enrolled in the study if they had atrial fibrillation (AF) or poor TTE window. We tried to eliminate AF as known predictors for recurrent strokes [3,4], and because in patients with AF there is difficulty in accurately assessing important TTE parameters like diastolic dysfunction, also we have to take the average measurements for more than one cardiac cycle for each TTE parameter. Patients were also excluded if they developed an acute cardiac event after admission with stroke and before TTE was done as this would affect TTE findings. Other exclusion criteria included intracererbral bleeding of any type, hemorrhagic strokes, brain tumors, brain vascular lesions, or other brain masses, patients admitted with transient ischemic attack and those who refused to be enrolled in the study.

Ischemic stroke is defined by symptoms and rapidly developing signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), due to disturbance in the blood supply to the brain caused by blockage (thrombosis, arterial embolism) [5,6]. Recurrent stroke was defined as a new cerebrovascular event that met one of the following criteria: 1) the event resulted in a neurological deficit that was clearly different from that of the index stroke; 2) the event involved a anatomic site or vascular territory different from that of the index stroke; 3) the event was of a stroke subtype different from that of the index stroke [7,8]. The diagnosis of ischemic stroke was confirmed both by clinical presentation and neuroimaging. Patients were diagnosed clinically by their treating physician and the diagnosis was verified by a neurology specialist.

The basic demographic data and clinical cardiovascular risk factors were collected using a standardized case randomized form, including age, sex, smoking status (including shisha), hypertension, diabetes mellitus, hyperlipidemia, family history of atherosclerotic vascular diseases (coronary artery diseases, stroke, peripheral vascular disease) personal history of coronary artery disease, diagnosed peripheral vascular diseases and chronic kidney disease. All patients underwent brain computer tomography which confirmed the diagnosis of ischemic stroke. Patients with lacunar infarctions, large vessel infarctions or both were included in the study.

Complete TTE studies were done for all patients by two cardiology specialists not involved in patient treatment or care and all echocardiographic findings were collected using a standardized case randomized form. All normal and abnormal TTE findings were interpreted according to the recommendations of American Society of Echocardiography [9]. Both echocardiographic findings and clinical risk factors were compared between both patient groups. Other additional investigations were carried out at the discretion of the treating physician like carotid doppler imaging, transoesophageal echocardiography (TEE), magnetic resonance imaging, and magnetic resonance angiography.

3. STATISTICAL ANALYSIS

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 20 for Windows. Entered data were checked for accuracy then for normality, using Kolmogorov-Smirnov & Shapiro-Wilk tests. Qualitative variables were expressed as numbers and percentages, while quantitative variables were expressed as means ± standard deviation (SD). Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances. The χ^2-test (or likelihood ratio = LLR) was used as a non-parametric test of significance for comparison between the distributions of two qualitative variables.

The Fisher's exact test was used as a non-parametric test of significance for comparison between the distributions of two qualitative variables whenever the χ^2-test was not appropriate. Logistic regression model for factors significantly predicting the recurrence of stroke was also used. A 5% level was chosen as a level of significance in all statistical significance tests used.

4. RESULTS

4.1. Baseline Clinical Characteristics

The study population included 217 patients (110 patients with first ischemic stroke and 107 patients with recurrent ischemic stroke) aged between 26 and 82 years. Mean age was 55 ± 12 years. The majority were men (155 patients, 71.4%).

As regard the clinical risk factors in all the study population, 83 patients (38.2%) were smokers, 120 patients (55.2%) had diabetes mellitus, 163 patients (75.1%) had hypertension, 140 patients (64.5%) had hyperlipidemia, 50 patients (23%) had family history of atherosclerotic vascular disease, 33 patients (15.2%) had coronary artery disease, 5 patients (2.3%) had diagnosed peripheral vas-

cular disease and 15 patients (6.9%) had chronic kidney disease.

Table 1 compares the baseline clinical characteristics between the two groups.

Hypertension was found in 70 patients (63.6%) in first stroke group compared to 93 patients (86.9%) in recurrent stroke group (OR, 3.79; 95% CI 1.91 - 7.71; p = 0.001), hyperlipidemia was found in 55 patients (50%) in first stroke group compared to 85 patients (79.4%) in recurrent stroke group (OR, 3.68; 95% CI 2.12 - 7.03; p = 0.001), family history of atherosclerotic vascular disease was found in 16 patients (14.5%) in first stroke group compared to 34 patients (31.8%) in recurrent stroke group (OR, 2.73; 95% CI 1.40 - 5.33; p = 0.003), coronary artery disease was found in 10 patients (9.1%) in first stroke group compared to 23 patients (21.5%) in recurrent stroke group (OR, 2.73; 95% CI 1.23 - 6.07; p = 0.011). Diagnosed peripheral vascular disease was absent in patients of first stroke group while present in five patients (4.7%) in recurrent stroke group and chronic kidney disease was found in two patients (1.8%) in first stroke group compared to 13 patients (21.1%) in recurrent stroke group (OR, 7.46; 95% CI 1.64 - 33.94; p = 0.003).

Despite the higher prevalence of diabetes mellitus in recurrent stroke group, in comparison with the first stroke group (61.7% versus 49.1% respectively), no statistical significant difference was found between both groups (p = 0.062). Only history of smoking was higher in first stroke group, in 49 patients (44.5%) compared to 34 patients (31.8%) in recurrent stroke group but without statistical significant difference (p = 0.053). Patients in first stroke group were significantly younger than in recurrent stroke group (52 ± 12 years versus 59 ± 11 years, p = 0.001).

4.2. Echocardiographic Findings

Abnormal TTE findings were found in 164 patients (75.6%). TTE findings in both groups are summarized in (Table 2). Three abnormal TTE findings were signifi-cantly higher in the recurrent stroke group; namely Left ventricular diastolic dysfunction that was found in 42 patients (37.1%) in first stroke group compared to 67 patients (62.7%) in recurrent stroke group (OR, 2.71; 95% CI 1.56 - 4.69; p = 0.001). LVH was found in 22 patients (20%) in first stroke group compared to 53 patients (49.5%) in recurrent stroke group (OR, 3.92; 95% CI 2.15 - 7.16; p = 0.001). Aortic sclerosis was found in 6 patients (5.5%) in first stroke group compared to 15 patients (14%) in recurrent stroke group (OR, 2.82; 95% CI 1.05 - 7.58; p = 0.003).

The mean of ejection fraction in first group was 61% ± 9% and was 59% ± 10% for recurrent stroke group, how-ever without statistical significant difference (p = 0.188). Despite the presence of other TTE abnormal findings in both groups such as LV systolic dysfunction in 16 pa-tients (14.5%) in first stroke group compared to 24 pa-tients (22.4%) in recurrent stroke group (p = 0.13), left atrial enlargement in 21 patients (19%) in first stroke group compared to 28 patients (26.1%) in recurrent stroke group (p = 0.21), left ventricular dilatation in 8 patients (7.3%) in first stroke group compared to 12 pa-tients (11.2%) in recurrent stroke group (p = 0.31), re-gional wall motion abnormalities in 11 patients (10%) in first stroke group compared to 15 patients (14%) in prior stroke group (p = 0.36), mitral regurgitation in 13 pa-tients (11.8%) in first stroke group compared to 18 pa-tients (16.8%) in recurrent stroke group (p = 0.29), tri-cuspid regurgitation in 9 patients (8.2%) in first stroke group compared to 13 patients (12.2%) in recurrent stroke group (p = 0.33), LV Thrombus was found in one patient only in each group, none of these findings had significant statistical difference between both groups nor predict recurrent strokes.

In multivariate analysis, older age (OR = 1.03; 95% CI,1.01 - 1.07; p = 0.002), hypertension (OR = 2.25; 95% CI,1.03 - 4.92; p = 0.002) and hyperlipidemia (OR = 2.73; 95% CI,1.07 - 5.35; p = 0.002), were statistically significant independent clinical predictors of recurrence of stroke (Table 3). Despite that the three abnormal TTE

Table 1. Demographic and clinical characteristics of study population.

Characteristic	First ischemic stroke (n = 110)	Recurrent ischemic stroke (n = 107)	P
Age (mean ± SD (years)	52 ± 12	59 ± 11	0.001
Male sex	82 (74.5%)	73 (68.2%)	0.303
Smoking (including shisha)	49 (44.5%)	34 (31.8%)	0.053
Diabetes mellitus	54 (49.1%)	66 (61.7%)	0.062
Hypertension	70 (63.6%)	93 (86.9%)	0.001
Dyslipidemia	55 (50%)	85 (79.4%)	0.001
Family history of atherosclerotic vascular disease	16 (14.5%)	34 (31.8%)	0.003
CAD	10 (9.1%)	23 (21.5%)	0.011
PVD	0 (0%)	5 (4.7%)	0.028
CKD	2 (1.8%)	13 (21.1%)	0.003

SD = Standard deviation, CAD = Coronary artery disease; PVD = Peripheral vascular Disease, CKD = chronic kidney disease.

Table 2. Echocardiographic findings of the study population.

Echocardiographic Findings	First ischemic stroke (n = 110)	Recurrent ischemic stroke (n = 107)	P
LVEF mean ± SD %	61% ± 9%	59% ± 10%	0.188
left ventricular systolic dysfunction	16 (14.5%)	24 (22.4%)	0.134
left ventricular diastolic dysfunction	42 (37.1%)	67 (62.7%)	0.001
left ventricular hypertrophy	22 (20%)	53 (49.5%)	0.001
Left ventricular dilatation	8 (7.3%)	12 (11.2%)	0.316
Left atrial enlargement	21 (19%)	28 (26.1%)	0.213
Right atrial enlargement	0 (0%)	1 (0.9%)	0.493
Right ventricular enlargement	0 (0%)	1 (0.9%)	0.493
Aortic sclerosis	6 (5.5%)	15 (14%)	0.033
Aortic stenosis	1 (0.9%)	6 (5.6%)	0.063
Aortic regurgitation	8 (7.3%)	8 (7.5%)	0.954
Mitral stenosis	1 (0.9%)	3 (2.8%)	0.365
Mitral valve prolapse	0 (0%)	1 (0.9%)	0.493
Mitral regurgitation	13 (11.8%)	18 (16.8%)	0.292
Tricuspid regurgitation	9 (8.2%)	13 (12.2%)	0.333
Pulmonary hypertension	6 (5.5%)	6 (5.6%)	0.961
Aortic dilatation	1 (0.9%)	0 (0%)	1.000
Pericardial effusion	1 (0.9%)	3 (2.8%)	0.365
Regional wall motion Abnormalities	11 (10%)	15 (14%)	0.362
Atrial septal defect	0 (0%)	0 (0%)	-
Patent foramen ovale	3 (2.7%)	0 (0%)	0.247
Interatrial septal aneurysm	2 (1.8%)	1 (0.9%)	1.000
Other cardiac defects	1 (0.9%)	0 (0%)	1.000
Left ventricular thrombus	1 (0.9%)	1 (0.1%)	1.000
Intracardiac masses	0 (0%)	1 (0.9%)	0.129

LVEF = left ventricular ejection fraction, SD = Standard deviation.

Table 3. Logistic regression model for factors predicting the recurrence of stroke.

Predictors	Odds ratio	95% CI
Age	1.03[*]	(1.01 - 1.07)
Hypertension	2.25[*]	(1.03 - 4.92)
Hyperlipidemia	2.73[*]	(1.40 - 5.35)
left ventricular hypertrophy	3.50[*]	(1.69 - 7.23)
left ventricular diastolic dysfunction	1.42	(0.74 - 2.76)
Aortic sclerosis	3.30	(0.37 - 29.61)
Left ventricular dilatation	1.88	(0.53 - 6.63)
left ventricular systolic dysfunction	0.99	(0.95 - 1.02)
Left atrial enlargement	0.62	(0.27 - 1.39)

[*] = significant at 5% level.

findings; namely LV diastolic dysfunction, LVH and Aortic sclerosis, using bivariate analysis, were significantly higher in prior stroke group, only LVH in multivariate analysis (OR = 3.5; 95% CI, 1.69 - 7.23; p = 0.002), was the significant echocardiographic predictor for recurrence of strokes (**Table 3**). It should be noted that all other variables entered in this model were not significant predictors for recurrence of strokes. These are left ventricular diastolic dysfunction, Aortic sclerosis, Left ventricular dilatation, left ventricular systolic dysfunction, and Left atrial enlargement (p-values were > 0.05).

5. DISCUSSION

In this study three TTE abnormalities (LV diastolic dysfunction, LVH and aortic sclerosis) were significantly higher in recurrent stroke group than in those with first stroke group. Adjusted analysis showed only LVH was a predictor for recurrence of ischemic strokes.

Transthoracic echocardiography is part of the routine workup of stroke patients in many centers across the world, to look for a cardiac source of embolus [10,11]. However, there is an ongoing debate regarding the cost effectiveness of this diagnostic tool. Most studies on the role of echocardiography on the management of acute stroke patients had focused on the capacity of TTE or transesophageal echocardiography to find potential sources of embolism [12-14]. Although cardioembolism might be responsible for 15% to 20% of ischemic strokes, the majority of patients undergoing TTE had no findings sug-

gestive of cardioembolism [15]. A recent hospital-based study from Canada reported that TTE has a low yield, diagnosing only 4% of ischemic stroke patients with abnormalities suggesting cardioembolic etiology [16]. Other cardiac structural and functional abnormalities that had been associated with cardioembolic stroke include LA dilatation, poor LV systolic function, valvular heart diseases, cardiac tumors, patent foramen ovale and atrial septal defect [17-19]. Instead of just focusing on finding potential sources of embolism, our study focused on finding other additional abnormalities that may help predict recurrence of ischemic strokes with difference between the two focuses.

In our study three in four patients had abnormal TTE findings. From these findings LV systolic dysfunction, LA enlargement, LV dilatation, regional wall motion abnormalities and mitral regurgitation. LV systolic dysfunction was found in 16 patients (14.5%) in first stroke group compared to 24 patients (22.4%) in recurrent stroke group (P = 0.13), left atrial (LA) enlargement was found in 21 patients (19%) in first stroke group compared to 28 patients (26.1%) in recurrent stroke group (P = 0.21), left ventricular dilatation was found in 8 patients (7.3%) in first stroke group compared to 12 patients (11.2%) in recurrent stroke group (P = 0.31), regional wall motion abnormalities was found in 11 patients (10%) in first stroke group compared to 15 patients (14%) in recurrent stroke group (P = 0.36), mitral regurgitation was found in 13 patients (11.8%) in first stroke group compared to 18 patients (16.8%) in recurrent stroke group (P = 0.29), none of these findings had significant statistical difference between both groups nor predict recurrent strokes.

In another study LV systolic dysfunction was a powerful, consistent, and independent predictor of stroke in patients with AF despite neither LA diameter nor mitral regurgitation was significantly associated with risk of stroke in this study [20]. In the study of Gambini and Paciaroni, LA diameter was significantly associated with the combined end point of ischemic stroke and systemic emboli [21]. However, it was not predictive of stroke in another larger cohort of patients with AF given aspirin in the SPAF study [22]. In both these studies, LV dysfunction emerged as a powerful independent risk factor for stroke[21,22].

In our study population group 38.2% were smokers, 55.29% had diabetes mellitus, 75.1% had hypertension, and 64.5% had hyperlipidemia. Among these risk factors only older age, hypertension and hyperlipidemia were significant clinical predictors for recurrence of strokes. The most relevant predictors of stroke recurrence identified in epidemiological trials include advancing age, arterial hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia [3,4]. A previous study suggested that clinical risk factors as hypertension, diabetes mellitus,

hyperlipidemia, ischemic heart disease, atrial fibrillation, smoking and carotid stenosis were contributing factors for stroke disease [23]. However, the minor differences in the prevalence of stroke risk factors in different communities are probably due to differences in culture, disease patterns, living habits and distribution of various ethnic groups. The clinical factors that were independently associated with stroke in the analysis of patients in a prospective study of patients from three clinical trials with full echocardiographic evaluations were increasing age, previous TIA or stroke, history of diabetes, or history of heart failure [20]. In agreement with our study, other studies have shown that all the above risk factors are more prevalent among male subjects [24-26]. Similar to our study, older studies showed that stroke prevalence rises with older age group [27]. With advancing age, the effect of increasingly high frequency of contributing factors such as hypertension, diabetes and hyperlipidemia might be a reason for the increased prevalence of stroke [24,28].

In our study hypertension was the first common risk factor as was present in 75.1% of our patients. Valery *et al* from Russia found 84.8% of their patients had hypertension [29]. Ong and Raymond from Singapore found 71.5% of their patients had hypertension [30]. In our study hyperlipidemia was the second most common risk factor, as was present in 64.5% of our patients with significant higher prevalence in recurrent stroke group, and this was higher than that reported in other studies [23]. In our study diabetes was the third most common risk factor as was present in 55.2% of all patient with significant higher prevalence in recurrent stroke group, this was also higher than reported in other industrialized countries where varied from 7% to 41%, in addition, researchers believed that diabetic patients are at an increased risk for hypertension and stroke [30,31].

In our study 38.2% were smoker and was higher in first stroke group who are younger than in recurrent stroke group which may furthermore contribute to uncommon etiologies in younger patients. The mechanisms by which cigarette smoking is thought to increase the likelihood of ischemic stroke include increased fibrinogen levels, platelet adhesiveness and reduced cerebral blood flow due mainly to atheroma formation associated with smoking and higher blood viscosity in chronic smokers [32,33]. The main limitation of this study was the relatively small number of patients examined and TTE findings were not corrected for body surface area which was difficult to assess due to difficult mobility in stroke patients with residual neurological deficits and disabilities.

6. CONCLUSION

Transthoracic echocardiography is a valid diagnostic modality for stroke workup and should be considered as an

essential test in all ischemic stroke patients. In patients with recurrent ischemic strokes who have sinus rhythm, among TTE abnormalities only LVH was a significant predictor for recurrence of ischemic strokes. Patients with recurrent ischemic strokes tended to be older with more clinical risk factors, among which aging, hypertension and hyperlipidemia were predictors for recurrent ischemic strokes. Those patients need more aggressive lipid lowering therapy and optimal control of blood pressure. Further studies with a larger sample size are needed to provide more supporting results to our study.

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