Risk Factors for Ischaemic Stroke in an Omani Community

A case-control study

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Abstract

Objectives: Stroke is recognized to be the third most common cause of mortality, with increasing incidence among developing countries. Recognition and control of risk factors is of prime importance in the prevention of stroke. We aimed to study the characteristics of ischemic stroke (IS) patients in Oman, and quantify its various risk factors using a case-control model. Methods: This study conducted from January 2012 to March 2013 included 255 adult Omani patients with IS admitted to two premier hospitals in Oman, compared to 255 age- and gender-matched controls. Demographic factors and frequency of various conventional risk factors were documented. Univariate and step-wise multivariate logistic regression analysis were performed to evaluate the risk factors associated for IS. Results: Of the 255 cases, 63% were males. The mean age was 62.2 ± 13.2 years. Most of the cases (89%) were above 45 years of age. Cardio-embolism(32%) was the commonest mechanism of IS. The stepwise multiple logistic regression model revealed that family history of stroke was the strongest independent risk factor with odds ratio (OR) of 10.10, followed by hypertension with
OR of 5.17 and high-density lipoprotein with OR 3.34 (p< 0.01). **Conclusions:** Cardio-embolism was the predominant mechanism of IS in this study. Family history of stroke, hypertension and reduced high-density lipoprotein were the leading independent risk factors. Strong emphasis on screening for risk factors, control of hypertension and lifestyle modification for those with family history of stroke, would be expected to emerge as the major stroke-preventive measures in Oman.

**Keywords:** Ischemic stroke; Risk factors; Case-control study; Oman.

**Advances in knowledge**
- In the context of rising prevalence of stroke in many developing countries, recognition of the predominant risk factors in a community is of prime importance. This study observed cardio embolism to be the predominant cause of ischemic stroke in Omani subjects, with family history of stroke, hypertension and dyslipidemia as the most prevalent risk factors.

**Application to patient care**
- Ischemic stroke in Omani populations shows a significant association with family history of stroke and hypertension as predominant risk factors.
- Cardio embolism being a major mechanism of IS in Oman, investigations to recognize cardiac dysrhythmias and valvular heart diseases should be routine part of stroke evaluation.
- Preventive measures aimed at reducing incidence of ischemic stroke in Oman should focus on modifiable risk factors such as hypertension, dyslipidemia and lifestyle modification (eg. for control of smoking, increasing physical activity).

**Introduction**
The global burden of stroke is increasing despite the declining stroke mortality rates. A more comprehensive approach to primary prevention of stroke is required, which targets individuals at all levels of risk and is integrated with prevention strategies for other diseases that share common risk factors. Ischemic stroke (IS) is a heterogeneous multifactorial disorder recognized by the sudden onset of neurologic deficits secondary to a vascular obstruction, with its varied manifestations determined by the location of injury in the brain. While the burden of ischemic stroke is recognized to be gradually
reducing in several developed nations, most developing countries are recognized to have an increasing incidence. The high domestic and global burden of ischemic stroke makes it an important public health concern. 

Stroke-related deaths in Oman contribute to about 11% of the total deaths, with the age-adjusted death rate being 73.29 per 100,000 populations. It is the third leading cause of mortality in Oman, after coronary heart disease and diabetes mellitus. Oman, similar to Middle Eastern population, has a relatively higher load of conditions predisposing to cardiovascular disease – hypertension, obesity, diabetes mellitus and dyslipidemia. Preliminary observations from a hospital based stroke registries in Oman as well as in the GCC countries suggest that stroke occurs about a decade earlier in Omani population as compared to Western cohorts. In this context, it is important to examine the actual risk factors of stroke in this population, so as to inform which preventive measures may need to be pursued with greater emphasis for stroke prevention. To our knowledge, no studies have hitherto addressed prevalence of IS or a formal quantification of risk factors associated with IS in Oman. This hospital based case-control study was conducted to study the characteristics of IS as well as to investigate and quantify the risk factors associated with IS among Omani patients, using a case-control design.

Methods

Study design and subject recruitment

This prospective, hospital based case-control study was conducted from January 2012 to March 2013 on Omani patients with IS admitted to two premier hospitals in the Sultanate of Oman namely, Sultan Qaboos University Hospital (SQUH) and the Royal Hospital, Muscat. Both the hospitals serve as national referral centers for specialized treatment of all types of stroke from all over the Sultanate, and have similar referral patterns. Subjects aged 18 years and above, who were newly diagnosed to have IS and admitted to the hospital were recruited as ‘cases’. IS was defined as the occurrence of acute focal neurologic deficits confirmed to be due to a vascular insult by clinical examination and brain computed tomography (CT) and/or magnetic resonance imaging (MRI). IS subtypes were defined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria. This is a widely used classification with good reliability and high sensitivity and specificity. Five subtypes of IS were recognized:
Large-artery atherosclerosis (LAA), Small-vessel disease or lacunar stroke (LS), cardio-embolic stroke (CE), stroke of other defined etiologies (OD) or stroke of other undetermined etiology (UD). Conditions mimicking IS such as intracerebral hemorrhage, cerebral venous sinus thrombosis, brain tumours, demyelinating condition – were excluded.

Control subjects included patients admitted to the same hospitals with non-medical conditions or for elective non-neurologic surgeries such as hernia, cataract etc. None of the controls had a history of stroke, either currently or in the past based on detailed documented medical evaluation. The controls were matched for age (±2 years) and gender.

The information collected from cases included demographic characteristics, IS subtypes, risk factors, medical comorbidities, laboratory tests, duration of hospital admission and outcomes namely, death, survived or left against medical advice (LAMA). Face-to face interviews of admitted subjects/knowledgeable relatives (or telephonic interviews as required) helped to complete the missing information if any. Information obtained from control subjects included demographics and presence of risk factors.

**Estimation of sample size**
Sample sizes for the cases and controls were estimated using the method as suggested by Schlesselman. For this, we considered the prevalence of hypertension as prime exposure rate in controls as 20% and the risk of developing stroke in exposed subjects with odds ratio (OR) of 2.0 with 95% confidence and 80% power; the sample sizes for the cases and controls were estimated at 255 each.

Risk factors of IS studied included: hypertension, diabetes mellitus, dyslipidemia, cardiac diseases, family history, smoking, alcohol, physical activity and obesity. Conventional definitions of risk factors were used for the purpose of this study. Briefly:

- Hypertension was defined as systolic blood pressure (SBP) of ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg or current use of antihypertensive medicines.
• Individuals who were on anti-diabetic drugs or having fasting blood glucose (FBS) of ≥ 7.0 mmol/L or HbA1c > 6.5 were considered having diabetes mellitus.

• Dyslipidemia was defined as the presence of one or more of the following: total cholesterol (TC) as ≥ 5.2 mmol/L; HDL cholesterol (HDL_C) as < 1.03 mmol/L; LDL cholesterol (LDL_C) as ≥ 3.4 mmol/L; triglycerides (TG) as ≥ 1.7 mmol/L.

• Cardiac disease was defined as the presence (in the past or currently) of a cardiac condition such as atrial fibrillation, ischemic heart disease, cardiomyopathy or valvular heart disease, which is considered a risk factor for ischemic stroke.

• Family history of IS was recognized when the subject had a first-degree relative (maternal, paternal or sibling) with a diagnosis of stroke.

• Individuals, who were not doing regular exercise for at least 20 minutes 3 times a week, were considered as lacking physical exercise.

• The body mass index (BMI) was calculated as weight/height² (kg/m²), and overweight was defined based as a BMI ≥ 30 kg/m².

• A history of smoking and alcohol consumption history were classified as binary exposure variables – based on any use currently or in the past vs never used.

Statistical Analysis
Continuous variables were expressed as means and standard deviations, and categorical variables as numbers and percentages. Significant differences between cases and controls for various categorical variables were explored using chi-square test. The relationship between the different risk factors and development of stroke were estimated using univariate analysis and was expressed in terms of crude odds ratios (ORs) with their 95% confidence intervals. A multivariable logistic regression model was fitted to investigate the association between the significant factors found under the univariate analysis and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) were obtained, using backward conditional multiple logistic regression analysis. The analyses were carried out using SPSS software. A p-value less than 0.05 (2-tailed tests) was considered as statistically significant.
The Medical Research and Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, approved the study. All participants gave their written informed consent prior to participating in the study.

Results
Baseline and clinical characteristics of the 255 cases are shown in Table 1. The ratio of males to females among cases is 1.7:1. Their ages ranged from 22 to 90 years, with a mean of 61.9 ± 13.3 years. Male and female patients were comparable in their mean ages (p=0.54). A majority of the cases (89%) were in the age group above 45 years. 234 (91.8%) patients were recruited from Royal Hospital and 21 (8.2%) from Sultan Qaboos University Hospital.

Among patients with ischemic stroke, cardio-embolism was the commonest mechanism (31.76%) followed by large artery atherosclerosis (28.24%). On sub-group analysis, cardio-embolic stroke was the predominant subtype among the subjects < 65 years old (34.5%) followed by stroke due to small artery occlusion in 26.2%. In contrast, among older patients, large artery atherosclerosis was the main subtype, accounting for 37.3%. Among the cases of IS, 14.51% had a history of TIA. The prevalence of TIA among males was 15.0% and in females 16.7% with no significant difference (p=0.73). About 35% of the patients had a previous history of one or more episodes of stroke.

Prevalence of various risk factors among the IS cases and controls and the crude odds ratios are shown in Table 2. Family history of stroke in first-degree relatives was the strongest independent risk factor, with odds ratio 8.08 (95% CI: 3.54, 18.41), followed by hypertension with OR 5.18 (95% CI: 3.50, 7.67). Decreased level of HDL_C as well as higher LDL_C and TC levels were noted among the cases as compared to the controls with ORs as 3.18 (95% CI: 2.14, 4.72), 2.12 (95% CI: 1.44, 3.11) and 1.68 (95% CI: 1.15, 2.45) respectively (p< 0.01). However, the level of triglycerides (TG) was not significantly associated with IS (p=0.281). Other risk factors namely, ischemic heart disease and diabetes mellitus were also found to be associated with the IS with odds ratios 2.67 (95% CI: 1.66, 4.24) and 2.05 (95% CI: 1.44, 2.92) respectively. Among life-style practices, lack of physical exercise, history of alcohol consumption and history of smoking were observed to be more prevalent among the cases as
compared to the control subjects with odds ratios 2.54 (CI: 1.70, 3.78), 2.17 (CI: 1.13, 4.17) and 1.84 (1.18, 2.87) respectively (p< 0.05).

Estimation of adjusted odds ratios based on step-wise multiple logistic regression analysis reconfirmed family history of stroke to be the strongest independent risk factor with OR 10.10 (CI: 3.41, 29.98), followed by hypertension with OR 5.17 (95% CI: 2.92, 9.14) and HDL_C with OR 3.34 (95% CI: 1.93, 5.78) (Table 3).

**Discussion**

Stroke is a common non-communicable disease and has a variable profile of risk factors among different communities. Using a case-control model, as in the current study, is a valid method of exploring risk factors of stroke. A case control model of study was chosen as it provides an opportunity to quantify the burden of various risk factors present in patients with stroke in comparison with controls in terms of odds ratio; it is also inexpensive and easier to conduct. In contrast, a cross sectional study, would entail the study of a larger number of patients but would provide prevalence measures though with poorer differentiation of cause-effect relationship.

Several of the observations in this study are comparable to those in recently published literature on IS within the region. The mean age of IS cases in our study is similar to mean of 64.1±10.4 years observed in the OPTIC Registry and 66.2±7.2 years in PERFORM Trial. Although in this study, IS due to cardio-embolism was more prevalent than that reported in other Arab studies, prevalence of heart disease and atrial fibrillation were found to be similar. Large artery stroke is often the more prevalent subtype; this however had a slightly lower prevalence than CE in this study. The most likely reason for this discrepancy may be sampling bias. While most patients with IS had tests performed to recognize cardio-embolic source (viz. Holter study and echocardiography), their interpretation was fairly uniform and was considered unlikely a factor in the above variance.

Data also revealed that cardio-embolism to have the worst outcomes among IS, with a higher fatality. This is recognized in several earlier studies also and it is mainly related to its pathophysiology: cardio-embolic stroke is often associated with relatively larger infarctions consequent to major vessel occlusion by the thrombus.
Modifiable risk factors play an important role in the development of stroke.\textsuperscript{20} Prevalence of different risk factor of IS varies among populations. The overall prevalence of risk factors in our study appears similar to those reported from a stroke registry cohort from Oman as well as in the GCC region.\textsuperscript{5,6} In agreement with GCC registry, the current study observed hypertension and dyslipidemia to have higher prevalence in IS as compared to controls.\textsuperscript{6} Hypertension was nearly two times more prevalent among IS patients as compared to controls. This exceeds the range reported from other Arab countries but is comparable to stroke patients from other Asian population such as Pakistan.\textsuperscript{21} In contrast, diabetes mellitus despite being observed to be significantly associated with IS on univariate analysis, did not emerge as a significant risk factor on multivariate analysis in our study. A possible reason for this is the overall higher prevalence of diabetes mellitus in the control population also. This observation may be supported by reports of relatively high prevalence of diabetes mellitus among adults in Oman.\textsuperscript{22}

The strongest risk factor for IS observed in this study was family history of stroke in first degree relatives, with a proportion nearly similar to that observed studies from United Arab Emirates (20\%) and Saudi Arabia (14.1\%). The relatively higher proportion of consanguinity in Oman may explain this observation.\textsuperscript{21,22} This observation may have several implications. The relatively high familial burden of stroke noted in this study may indeed point to specific genetic factors underpinning atherosclerotic disease in the Omani population. Other possibilities are a stronger genetic predisposition to vascular risk factors such as hypertension or dyslipidemias indirectly influencing stroke incidence, or rarely, prevalence of one or more specific single-gene mutations that are associated with stroke. This observation also suggests that studies such as genome-wide analysis involving a significantly large number of families with stroke burden may have a reasonable chance of recognizing such factors. Indeed few large, well-powered genome-wide association study analyses have uncovered significant associations in IS.\textsuperscript{5} The findings of a prospective hospital-based registry which collected data from four countries in Arabian Gulf Countries also supports the concept that IS is a poly-etiologic disease and that race/ethnic differences and genetic factors may be the reasons for the differences between Arab populations and Western registries.\textsuperscript{6} An effort towards exploring a genetic basis of IS has been
initiated at our center in the form of genetic analysis of apolipoprotein profile using a case-control design. An ongoing stroke registry also aims to include genetic studies.

Many factors ranging from differences in physical activity and nutrition patterns\textsuperscript{25} to genetic predisposition\textsuperscript{26} are likely to contribute to the higher prevalence of diabetes and obesity in this region. The large, multinational OPTIC registry and PERFORM trial observed a trend of higher frequency of conventional risk factors for stroke, as well as inadequately managed diabetes mellitus, hypertension, and tobacco smoking in patients from Arab countries.\textsuperscript{15} Though the significantly higher prevalence of diabetes mellitus among IS cases was noted in our study, diabetes mellitus and smoking were not found to be important risk factors on logistic regression analysis. Earlier studies have observed a younger age of occurrence of stroke in Arab countries.\textsuperscript{13} While 89\% of the cases in the present study were in the age group above 45 years, the mean age of IS patients is at least a decade less than that reported in Western populations. A larger study may be required to provide a plausible explanation for these findings related to diabetes, smoking and older age in our cases in our study.

This study has several limitations. The relatively small number of patients were sourced from two major health care institutions in the country, both located in the same city. This may limit generalization of the observations to more distant communities of the country. However, as noted, both serve the same population and have similar referral practices and hence were unlikely to recruit different patterns of cases in to the study. Familial occurrence of stroke could not be explored in detail with regard to patterns of inheritance, relation to risk factors, etc. Patients with TIA who were discharged early for outpatient follow could not be objectively assessed. While heart disease (inclusive of different conditions) as a risk factor was studied, certain risk factor such as atrial fibrillation or other specific heart diseases were not addressed in this study. Further well designed, comparative studies of Arabian populations with other ethnic communities are required to explore these concepts.

**Conclusion**

Ischemic stroke in Omani population shows a significant association with family history of stroke and hypertension as predominant risk factors. Cardio embolism being a major mechanism of IS in Oman, investigations to recognize cardiac dysrhythmias
and valvular heart diseases should be routine part of stroke evaluation. Preventive measures aimed at reducing incidence of ischemic stroke in Oman should focus on modifiable risk factors such as hypertension, dyslipidemia and life style modification (eg. for control of smoking, improving physical activity). Further studies exploring familial burden of stroke in Oman with modern genetic studies may provide an insight into possible gene based interventions for prevention of stroke as well as other related non-communicable disorders.

Conflict of Interest
The authors declare no conflicts of interest.

Funding
No funding was received for this study.

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Table 1: Baseline and clinical characteristics of Ischemic stroke patients (n=255)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Age in years Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>161</td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
</tr>
<tr>
<td>Age groups in years</td>
<td></td>
</tr>
<tr>
<td>18 – 45</td>
<td>28</td>
</tr>
<tr>
<td>46 – 65</td>
<td>117</td>
</tr>
<tr>
<td>&gt;65</td>
<td>110</td>
</tr>
<tr>
<td>Ischemic Stroke sub-type</td>
<td></td>
</tr>
<tr>
<td>LAA</td>
<td>72</td>
</tr>
<tr>
<td>CE</td>
<td>81</td>
</tr>
<tr>
<td>LS</td>
<td>61</td>
</tr>
<tr>
<td>OD</td>
<td>6</td>
</tr>
<tr>
<td>UD</td>
<td>35</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>At discharge</td>
<td>8</td>
</tr>
<tr>
<td>Three months follow-up</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
</tr>
<tr>
<td>Previous history of TIA</td>
<td>37</td>
</tr>
<tr>
<td>Previous history of stroke</td>
<td>91</td>
</tr>
</tbody>
</table>

LAA- Large Artery Atherosclerosis; CE- Cardio embolism; LS- Lacunar Stroke; OD – Other determined cause; UD- Undetermined cause; TIA- Transient ischemic attack.
Table 2: Prevalence of risk factors of ischemic stroke and their crude odds ratios among cases of ischemic stroke and controls.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cases (n=255) No. (%)</th>
<th>Controls (n=255) No. (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>*p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (HTN)</td>
<td>202(79.2)</td>
<td>108(42.3)</td>
<td>5.18</td>
<td>3.50, 7.67</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td>159(62.3)</td>
<td>114(44.7)</td>
<td>2.05</td>
<td>1.44, 2.92</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>173(67.8)</td>
<td>111(43.5)</td>
<td>2.73</td>
<td>1.91, 3.93</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Chronic kidney disease (CKD)</td>
<td>16(6.3)</td>
<td>13(5.1)</td>
<td>1.24</td>
<td>0.58, 2.64</td>
<td>0.566</td>
</tr>
<tr>
<td>Heart Disease (HD)</td>
<td>67(26.3)</td>
<td>30(11.8)</td>
<td>2.67</td>
<td>1.66, 4.24</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Smoking</td>
<td>69(32.9)</td>
<td>43(21.0)</td>
<td>1.84</td>
<td>1.18, 2.87</td>
<td>0.006*</td>
</tr>
<tr>
<td>No regular exercise</td>
<td>123(60.3)</td>
<td>76(37.4)</td>
<td>2.54</td>
<td>1.70, 3.78</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>30(14.6)</td>
<td>15(7.3)</td>
<td>2.17</td>
<td>1.13, 4.17</td>
<td>0.020*</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>40(37.4)</td>
<td>55(31.1)</td>
<td>1.32</td>
<td>0.80, 2.19</td>
<td>0.275</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>45(22.4)</td>
<td>7 (3.4)</td>
<td>8.08</td>
<td>3.54, 18.41</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TC (≥ 5.2 mmol/L)</td>
<td>108(47.8)</td>
<td>80(35.2)</td>
<td>1.68</td>
<td>1.15, 2.45</td>
<td>0.007*</td>
</tr>
<tr>
<td>HDL_C (&lt; 1.03 mmol/L)</td>
<td>119(52.9)</td>
<td>59(26.1)</td>
<td>3.18</td>
<td>2.14, 4.72</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDL_C (≥ 3.4 mmol/L)</td>
<td>112(50.2)</td>
<td>72(32.3)</td>
<td>2.12</td>
<td>1.44, 3.11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TG (≥ 1.7 mmol/L)</td>
<td>50(22.2)</td>
<td>41(18.1)</td>
<td>1.29</td>
<td>0.81, 2.05</td>
<td>0.281</td>
</tr>
</tbody>
</table>

BMI- Body Mass Index; TC- Total cholesterol; HDL_C – HDL Cholesterol; LDL_C – LDL Cholesterol; TG- Triglycerides.  *p= Significant at <0.05
Table 3: Results of multiple logistic regression analysis exploring the relationship of Ischemic stroke risk factors.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>10.10</td>
<td>3.41</td>
<td>29.98</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.17</td>
<td>2.92</td>
<td>9.14</td>
</tr>
<tr>
<td>No regular exercise</td>
<td>2.65</td>
<td>1.56</td>
<td>4.50</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>2.28</td>
<td>0.88</td>
<td>5.91</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>3.34</td>
<td>1.93</td>
<td>5.78</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>2.96</td>
<td>1.72</td>
<td>5.09</td>
</tr>
</tbody>
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