Reduced kidney function and outcome in acute ischaemic stroke: relationship to arterial hypertension and diabetes

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Abstract

Background. Stroke is a dangerous long-term complication of kidney failure, yet its occurrence early in disease is poorly characterized. Our aim was to investigate the association of reduced kidney function, hypertension and diabetes with acute ischaemic stroke and the outcome thereof.
Methods. In this prospective cohort study, the association of reduced kidney function, hypertension and diabetes with stroke and 2-year all-cause mortality was investigated. Glomerular filtration rate (eGFR) was estimated by the simplified Modification of Diet in Renal Disease formula in 13 365 consecutive patients (671 with acute ischaemic stroke) admitted to our clinical facility over a 12-month period.

Results. Ischaemic stroke, after adjustment for age and gender, was significantly associated with eGFR <60 mL/min/1.73m² [odds ratio (OR) 1.53, 95% confidence interval (CI) 1.30–1.81], hypertension (2.77, 95% CI 2.33–3.28) and diabetes (1.30, 95% CI 1.04–1.63). Multivariate analysis of interaction indicated the absence of an additive effect between eGFR, hypertension and diabetes, on the risk of stroke. Age and gender-adjusted survival analysis by Cox regression showed an association of mortality with reduced eGFR alone (HR = 4.29, 95% CI 1.02–19.60).

Conclusions. In patients acutely admitted to hospital, reduced kidney function, hypertension and diabetes are independently associated with ischaemic stroke, but do not exert a synergetic effect. After hospital discharge, mortality is strongly associated with reduced eGFR but with neither hypertension nor diabetes.

Keywords: ischaemic stroke; kidney dysfunction; mortality

Introduction

Although the prevalence of stroke in patients with chronic kidney disease (CKD) is higher than in the general population, renal dysfunction is not widely recognized as a risk factor for stroke [1, 2]. Besides, information on the relationship between CKD and stroke is not as complete as in the case of heart disease, and investigations have produced less clear-cut results [3]. Different subtypes of stroke have been analysed as a whole, and patients were mostly enrolled from different catchment areas. A major confounding factor in this type of study is the choice of the population being studied, namely general population versus ‘high-risk’ subjects. In fact, selection criteria of subjects from medical practice and federal population versus ‘high-risk’ subjects. In fact, selection criteria of subjects from medical practice and federal population versus ‘high-risk’ subjects. In fact, selection criteria of subjects from medical practice and federal population versus ‘high-risk’ subjects. In fact, selection criteria of subjects from medical practice and federal population versus ‘high-risk’ subjects.

The aim of our study was to investigate the association between kidney dysfunction with ischaemic stroke and to test the interaction of different degrees of renal impairment with the recognized risk factors, hypertension and diabetes. The study was performed in a cohort of patients, admitted to the same hospital over a 12-month period. All patients were from the same catchment area and the same laboratory according to a single methodology made all serum creatinine determinations. An analysis of the role of kidney function, hypertension and diabetes on post-ictus survival was also conducted.

Materials and methods

Design

The cohort study included 671 consecutive patients acutely admitted to the hospital for ischaemic stroke from 1 January 2007 to 31 December 2007. The Santa Maria Della Misericordia hospital in Perugia, Italy, collects all admissions of a catchment population of ~200 000 and is the core clinical facility for acute CV events in the area. The longitudinal study included 355 consecutive subjects of the above cohort who lived in the Perugia area and whose survival data were available. Patients were identified at hospital discharge by the electronic discharge form and then their survival was periodically checked. The follow-up ended 31 December 2009. Mortality data were obtained from the registry office of the local health authority.

Diagnosis

The diagnosis of ischaemic stroke and the presence of coexisting diseases were obtained using the hospitalization discharge diagnosis code of the International Classification of Disease (ICD-9). The selected ICD-9 codes for ischaemic stroke were 433, 434 and 436. The coexisting presence of diabetes and arterial hypertension was also recorded. The value of serum creatinine measured on admission was used for the study.

Laboratory.

A Shimadzu CL-7300 auto-analyser was used for all determinations of serum creatinine. The analysis was performed with the automated reaction-rate method of Jaffe (BioSystems S.A., Barcelona, Spain). The calibration was performed at the start and at the end of every session with a serum-based calibrator (Biochemistry Calibrator, cod. 18011; BioSystems S.A.)

The quality control was performed with the Biochemistry Control Serum levels 1 and 2 (BioSystems S.A.). The performances of the measurement procedure were as follows: linearity limit: 20 mg/dL of creatinine, repeatability (within run): mean concentration 1.7 mg/dL, CV 2.9%; mean concentration 5.3 mg/dL, CV 1.3% and reproducibility (run to run): mean concentration of 1.7 mg/dL, CV 3.9%; mean concentration 5.3 mg/dL, CV 2.9%. Normal values for laboratory were as follows: men, 0.9–1.3 mg/dL; women, 0.6–1.1 mg/dL. The method used does not have an isotope dilution mass spectrometry traceable standard; therefore, the old Modification of Diet in Renal Disease (MDRD) formula was used.

For every measurement of serum creatinine, the analyser reported the estimated glomerular filtration rate (eGFR). The eGFR was calculated with the four-variable (MDRD-4) formula: eGFR (mL/min/1.73m²) = 186 × (Scr)−1.154 × (age)−0.203 × (0.742 if female) × (1.212 if patients were black) [5]. On the basis of eGFR, patients were grouped using a modified National Kidney Foundation classification of CKD as follows: Group 1, eGFR >60 mL/min; Group 2, eGFR 46–60 mL/min (Stage 3a CKD); Group 3, eGFR 30–45 mL/min (Stage 3b CKD); Group 4; eGFR 15–29 mL/min (Stage 4 CKD); Group 5; eGFR <15 mL/min (Stage 5 CKD) [6]. Patients with a diagnosis of acute renal failure (ICD-9: 584) were examined separately. Group 1 (eGFR >60 mL/min) was used as a reference group for the analysis.

Age was also used for grouping, as follows: years <20 (Group 1), years 21–40 (Group 2), years 41–60 (Group 3), years 61–80 (Group 4) and years >80 (Group 5).

Survival

The primary outcome was death from any cause. Deaths occurring in hospital or within 45 days of admission were recorded as short-term mortality.

Statistical analysis

Data are reported as mean values ± SD, ranges or percentages. Comparisons between continuous variables were made by analysis of variance. Proportions were compared with the chi-square test, and the odds ratio (OR) with 95% confidence limits (CI) was assessed. The association of ischaemic stroke with the analysed variables (gender, age, diabetes, arterial hypertension and eGFR groups) was tested with logistic regression (forward stepwise). The interaction among reduced eGFR, diabetes and arterial hypertension was also assessed according to Andersson et al. [7]. We calculated the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) with 95% CIs. In this analysis, RERI >0 and AP >0 indicate additive interaction between the two examined variables.
Association of acute mortality with the predicting variables was analysed with logistic regression. Survival through the whole follow-up was assessed with the Kaplan–Meier method and the comparison made by log-rank test. Cox proportional hazard regression (forward stepwise) was used to assess the role of the different variables on survival. Hazard ratios (HRs), adjusted for age and gender, were calculated together with their 95% CIs. In the Cox model, eGFR was entered as a dichotomous variable: >60 and ≤60 mL/min/1.73m². All data management and statistical analysis were performed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL).

Results

During the 12 months, serum creatinine was measured in 13 365 consecutive patients admitted to the hospital; 671 (4.8%) were discharged with a diagnosis of ischaemic stroke. The clinical characteristics of the population are shown in Table 1. Compared to all admitted patients, those with stroke had a lower eGFR and were older. The prevalence of an eGFR <60 mL/min/1.73m² in patients with stroke was 43%, significantly higher than in other patients admitted to hospital. Likewise, the prevalence of male gender, diabetes and hypertension was higher in patients with ischaemic stroke. The grouping of stroke patients according to eGFR showed a significant difference in the composition only for age and gender and not for prevalence of diabetes and hypertension (Table 2). In women with reduced glomerular filtration rate (GFR) and stroke, the mean age was higher than in men (77.0 ± 13.8 versus 71.5 ± 14.5; P < 0.001). In the group of stroke patients with reduced eGFR aged >80, 63.5% were women (P < 0.001). Logistic regression with ischaemic stroke as a dependent variable was applied to the 13 365 admitted patients. The analysis produced a model with the following significant predictors: age (>52 years), male gender, hypertension and eGFR <60 mL/min. In the next step, eGFR was entered as a five-group variable and the significant association was found with the eGFR of 45–60 mL/min (Table 3). The analysis was repeated in patients without diabetes and hypertension. In this subgroup of ischaemic stroke (245 patients), an eGFR <60 mL/min was present in 101 cases (41.2%). The association was statistically significant (P < 0.001; OR 2.01, CI 1.72–2.34).

The test for interaction showed the absence of an additive risk between eGFR <60 mL/min, hypertension and diabetes.

Survival

In 355 patients with ischaemic stroke, survival data were available; 162 subjects had an eGFR <60 mL/min/1.73m². They were followed for a maximum of 34.1 months. The survival (mean ± SE) was 28.6 ± 0.6 months.

On the whole, 82 deaths were recorded; 26 within 45 days of admission. The analysis of this short-term mortality showed that only age (81.1 ± 12.7 years) was significantly associated with death (P < 0.001).

Cox regression analysis of survival was performed on the whole follow-up time. Age, gender, diabetes, hypertension and eGFR were entered as variables; the analysis produced a model with only age (>52 years) and eGFR <60 mL/min/1.73m² being significant predictors of death. The respective HRs were age 1.08, CI 1.05–1.11, P < 0.001 and eGFR (<60 mL/min/1.73m²) 4.29, CI 1.02–19.60, P = 0.045. Figure 1 shows the age- and sex-adjusted survival for patients according to eGFR.

Acute renal failure was diagnosed in 33 patients (19 deceased); in one case, the association with ischaemic stroke was present.

Discussion

Our study shows that, in a cohort of patients, of a single ethnicity and from the same area, admitted to the same hospital, ischaemic stroke was associated not only with the well-known risk factors, age, male gender, hypertension and diabetes, but also with reduced kidney function. The interaction between reduced kidney function and diabetes or hypertension did not significantly increase the risk associated with the individual variables. Age-adjusted reduced kidney function was also the main predictor for all-cause medium-term mortality.

Table 1. Clinical characteristics of patients with and without stroke

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>No stroke</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>671</td>
<td>12 694</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>73.3 ± 11.2</td>
<td>57.2 ± 22.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63.1</td>
<td>52.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)*</td>
<td>105.1 ± 38.0</td>
<td>98.1 ± 56.5</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)*</td>
<td>61.7 ± 15.3</td>
<td>75.9 ± 35.0</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min (%)</td>
<td>43.0</td>
<td>26.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>57.8</td>
<td>22.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16.5</td>
<td>9.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*aMean ± SD.

Table 2. Clinical characteristics of patients with ischaemic stroke according to the eGFR

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR mL/min/1.73m²</td>
<td>&gt;60</td>
<td>46–60</td>
<td>30–45</td>
<td>15–29</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Number (%)*</td>
<td>381 (3.9)</td>
<td>192 (8.9)</td>
<td>77 (7.9)</td>
<td>16 (4.3)</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.1 ± 11.5</td>
<td>76.3 ± 8.9</td>
<td>80.3 ± 8.2</td>
<td>75.8 ± 14.1</td>
<td>83.6 ± 3.0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>27.1</td>
<td>51.9</td>
<td>46.1</td>
<td>46.7</td>
<td>50</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>15.7</td>
<td>16.7</td>
<td>18.2</td>
<td>26.7</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>56.7</td>
<td>60.9</td>
<td>54.5</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>7.0 ± 7.2</td>
<td>7.1 ± 6.4</td>
<td>9.4 ± 10.9</td>
<td>7.2 ± 4.1</td>
<td>7.7 ± 3.0</td>
</tr>
</tbody>
</table>

*aPrevalence of stroke within the eGFR groups.
Ischaemic stroke and kidney dysfunction

Table 3. Predictors of ischaemic stroke by the logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≥52</td>
<td>3.18</td>
<td>2.30–4.32</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>1.51</td>
<td>1.27–1.80</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present</td>
<td>1.30</td>
<td>1.04–1.63</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present</td>
<td>2.77</td>
<td>2.33–3.28</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²) ≤60</td>
<td>1.53</td>
<td>1.30–1.81</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²) 45–60</td>
<td>2.76</td>
<td>1.03–7.65</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. 1. Cumulative 30 months survival in stroke patients according to eGFR. Plots of Cox regression, age and gender adjusted, for all-causes mortality. Probability value <0.001.

The association of stroke with high blood pressure is widely recognized and almost two-thirds of the stroke burden globally is attributable to non-optimal control of hypertension [8, 9]. Studies in patients with stroke of all types and hypertension have shown that associated risk factors influence stroke subtype; unfortunately, reduced kidney function was not analysed together with other risk factors [10]. The demonstration of an additive risk between kidney dysfunction and hypertension provides insight into the role of hypertension in ischaemic stroke. Yet, from our data, hypertension does not seem to have a role in its outcome, while reduced kidney function does. Previous studies have shown that patients with diabetes have a 1.5- to 3-fold increase in the risk of stroke when compared to the general population; but in most of the studies, the presence of kidney dysfunction in diabetic patients was not taken into consideration [11]. Our finding of a strong association of the female gender with stroke in presence of a reduced eGFR is, at least in part, explained by the higher age. The trend of increasing age in women with stroke has also been observed in the general population [12]. A limitation in our study is lack of data on acute treatment and other variables including smoking habit, dyslipidaemia, anaemia, all representing relevant factors in the pathogenesis and outcome of stroke. These data, as well as sequential measures of eGFR, could have been retrieved from patients files, but this procedure was ruled out at the planning of the study for the large total number of patients and controls and for the sake of simplicity. Acute kidney injury was not recorded at discharge and therefore we could not assess its role in the outcome [13]. Regarding assessment of kidney function, it is to be considered that different equations for the estimation of the eGFR have different sensitivities. The simplified MDRD formula, without creatinine calibration, has been ascribed with substantial errors for GFR estimates in the normal–high range and its use has been questioned for its impact on health services and for its utility in predicting mortality [14].

In our study, the determination of serum creatinine in a single laboratory with the same method might have helped reduce the inherent inaccuracy of the simplified MDRD formula. A recent reappraisal has established the good accuracy of the MDRD formula also in comparison with the more recent formulas [15]. Yet, when two of the most used formulas, MDRD and Mayo, were used in patients with stroke, in spite of their differences, both of them consistently showed a poor outcome as being associated with renal dysfunction [16].

While previous studies of association have examined ischaemic and hemorrhagic types of stroke, and sometimes also transient ischaemic attacks, we chose to analyse only ischaemic stroke to focus on a more homogenous sample and to reduce confounding factors [10, 17]. In spite of this, we must acknowledge that inaccuracy in the assignment of ischaemic stroke subtype with ICD-9 code has been reported to remain high [18].

We have not produced data explaining directly the association between reduced kidney function and ischaemic stroke but other studies have revealed many potential pathological links [19]. In our cohort, an eGFR of 45–60 mL/min was most significantly associated with stroke. This holds true for the group with relatively older women and this might represent a key to our results. On the other hand, this is not an advanced stage of kidney insufficiency and the pathological mechanisms of uraemia are not fully deployed. Therefore, the link is probably to be found in the early alterations of kidney dysfunction.

This finding has also an epidemiological relevance since it has been shown that this stage of kidney dysfunction is present in >3% of the general population and therefore represents a relevant risk factor [20]. The United States Renal Data System in its analysis of different databases showed an increased prevalence of stroke in patients with more advanced stages of CKD, especially in Stage 5 [21]. A relationship of baseline presence and severity of renal disease to long-term mortality in persons with self-reporting stroke has also been recently found [22]. Our population differs from these series for method of enrolment, hospital setting and type of stroke analysed. In fact, apart from haemorrhagic stroke, we have also excluded from the study patients with TIA or silent brain infarction [23]. Finally, our study is underpowered with respect to Stages 4 and 5 CKD.

In recent years, epidemiological studies on stroke have shown a stabilization or reversal in the declining secular (long-term) trends in the pre-1990s rates of incidence and prevalence, especially in older people and in women [24]. In the last decade, an increased prevalence of CKD has also been shown to occur [18]. Our data may suggest a relationship between the two epidemiological trends and point to
kidney dysfunction as one of the factors responsible for the poor outcome of patients with stroke. The clinical implication of our study is that monitoring kidney function may select subjects at high risk for ischaemic stroke needing more stringent blood pressure and glycaemic control. Patients with early stages of kidney dysfunction need close surveillance and the adoption of more severe preventive measures of ischaemic stroke.

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Conflict of interest statement. None declared.

References

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