Evaluation of Influence of Chronic Kidney Disease and Sodium Disturbances on Clinical Course of Acute and Sub-Acute Stage First-Ever Ischemic Stroke

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Background: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular morbidity and mortality. Hyponatremia is the most common electrolyte disturbance encountered in the neurological and neurosurgical intensive care units, and can exacerbate existing neurological deficits. The objective of this study was to observe the influences of chronic kidney disease and sodium disturbances on the clinical course of acute and sub-acute stages of first-ever ischemic stroke.

Material/Methods: 464 patients with previously diagnosed chronic kidney disease (aged 70.42±11.49 years; 250 women) who had experienced their first-ever ischemic stroke were qualified. The following examinations were performed: serum levels of sodium, creatinine, lipids, estimated glomerular filtration rate (eGFR), neurological state on 1st day of stroke (according to National Institutes of Health Stroke Scale), functional state measured with the Rankin scale, (RS) and mortality rate at 1 month after stroke.

Results: The neurological state on 1st day of stroke was worse and the median RS (30 days after stroke) was higher in patients with eGFR £ 60 ml/ (min×1.73). Men with eGFR £ 60 ml had greater neurological deficits and increased mortality within 1 month. In patients with eGFR >60 ml/, male sex was more often associated with worse outcomes at 1 month after ischemic stroke. Hyponatremia was associated with a more severe state in both the acute and sub-acute stages of stroke, with higher incidence of death within 1 month after stroke. Men with hyponatremia had greater neurological deficits on the 1st day and increased mortality within 1 month.

Conclusions: Renal impairment and hyponatremia are associated with worse neurological outcomes in patients in the acute stage of their first-ever stroke and within 1 month after the event. Males with impaired kidney function and hyponatremia have a more severe course in their first-ever ischemic stroke, as well as having increased mortality.

Keywords: Hyponatremia • Kidney Failure, Chronic • Stroke

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Background

Chronic kidney disease (CKD), the prevalence of which is estimated to be 8–16% worldwide, is an independent risk factor for morbidity and mortality in patients with cardiovascular disease [1]. Sodium is important in maintaining irritability and conduction of nerve and muscle tissues and assists in the regulation of acid-base balance. Hyponatremia is the most common electrolyte disorder encountered in patients in the neurological and cardiovascular systems. Hyponatremia is considered an independent risk factor for neurological and cardiovascular events [2–4]. Neurological disorders that cause hyponatremia are diverse and include trauma, subarachnoid hemorrhage, intracerebral hemorrhage, meningitis, and stroke [4–6]. One reason for the increased risk of cardiovascular disease in patients with chronic kidney disease is accelerated atherosclerosis. Advanced asymptomatic atherosclerosis in the carotid arteries is observed in patients during the early stages of CKD, with intima and media thickness increasing directly with a decline in glomerular filtration rate [7]. Concentric arterial calcification is associated with arterial stiffness, resulting in a high pulse pressure and increased characteristic aortic impedance. It has been observed that there is an association between intima-media thickness and increased incidence of ischemic stroke [8].

The aim of this study was to evaluate the influence of chronic kidney disease and sodium disturbances on the clinical course of acute and sub-acute stage of first-ever ischemic stroke.

Material and Methods

This prospective, non-randomized study, performed from January 2013 to July 2013, consisted of 464 patients aged 70.42±11.49 years (250 women) with previously diagnosed chronic kidney disease (according to KDIGO 2012 guidelines) [9] admitted to the Department of Neurology due to a first-ever ischemic stroke commensurate with the WHO criteria [10]. The study group consisted of patients in which computed tomography (CT) of the head, performed during the first 24 h of an ischemic event, did not reveal any abnormalities or only revealed early ischemic changes. Patients with both symptoms of transient ischemic attack (TIA) and intracranial hemorrhage, complicated by ischemic stroke due to vasospasm, were excluded from the study. Ethics committee approval was not required because the study was based on a routine laboratory tests performed in every patient with a stroke – no patient identification was recorded and thus the study did not fulfill the criteria of a medical experiment.

The patients were divided into 1 of 2 subgroups:

- a. depending on the value of eGFR: ≤60 ml/(min×1.73 m²) and >60 ml/(min×1.73 m²).
- b. depending on the sodium concentration: ≤135 mmol/l and >135 mmol/l.

The following parameters were analyzed:

- age at which first-ever ischemic stroke occurred;
- prevalence of comorbidities, such as hypertension, persistent atrial fibrillation, diabetes mellitus (DM), and dyslipidemia. Diagnosis of hypertension was consistent with the recommendation of the Polish Society of Cardiology [11]; DM was diagnosed according to the criteria of the Polish Diabetes Association (2013) [12]; dyslipidemia was defined as total cholesterol serum level >200 mg/dl (>5.18 mmol/l); or LDL-cholesterol serum level >100 mg/dl (2.59 mmol/l), or HDL-cholesterol serum level <35 mg/dl (0.91 mmol/l), or triglyceride serum level >135 mg/dl (1.53 mmol/l);
- neurological condition during the first 24 h of the ischemic event using the NIHSS score (National Institutes of Health Stroke Scale) [13] (the neurological state was assessed as good or moderate: 0–12 points in NIHSS and severe >12 points in NIHSS respectively);
- mortality rate at 1 month after their first-ever stroke;
- the status of functioning at 1 month after first-ever stroke measured by modified Rankin scale (mRS) [14] during control medical examination in hospital (the functioning state after stroke was assessed as good when the patient did not require caregiver assistance (0–3 points in mRS) or severe when the patient was dependent on the caregiver or died (4–6 points in mRS).

The acute phase of stroke was defined as a period of 1–7 days. The subacute period was defined as 1–3 weeks.

All parameters were also analyzed after the respondents were divided by sex.

Laboratory tests

Laboratory tests were conducted in the Central Laboratory of the Upper Silesian Medical Centre in Katowice. Venous blood samples (20 ml), taken on admission, were withdrawn into plastic test tubes (Vacutainer system). The tubes were allowed to clot, and then centrifuged at room temperature (1000 × G) for 10 min.

The spectrophotometric method (Point Scientific Inc., Michigan, USA) was used to determine the serum level of sodium (Na), glucose, creatinine, and lipids. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration [14].

Statistical analysis

All parametric values were expressed as mean with standard deviations (SD). All statistical analyses were performed using the STATISTICA 8.0 PL software. The distribution was analyzed using the Kolmogorov-Smirnov test. Because of the size of the
control group, the subgroups, and the nonparametric distribution of some of the parameters, the Mann-Whitney U test was used to compare the study groups and for age we used the t test. For categorical variables, we used chi-square tests. P<0.05 was considered statistically significant.

Results

The age of patients with their first-ever stroke and the prevalence of selected comorbidities (hypertension, atrial fibrillation, dyslipidemia and diabetes mellitus) did not differ in subgroups of patients with decreased eGFR ($\leq 60$ ml/(min×1.73 m$^2$)) (Table 1).

Neurological condition in the acute stage of a first-ever stroke, evaluated using the NIHSS score, was worse, and the average score in mRS (indicative of a greater degree of disability with in 30 days after stroke) was higher in patients with eGFR $\leq 60$ ml/(min×1.73 m$^2$) (Table 2). The mortality rate within 1 month did not differ in patients when divided according to eGFR (7% vs. 5%; p=0.4). Men with eGFR $\leq 60$ ml(/min×1.73 m$^2$) were characterized by greater neurological deficits on the first day of stroke and increased mortality within 1 month after a greater level of disability was observed in men with a normal serum sodium level (Table 5).

Discussion

CKD is a major risk factor for cardiovascular disease, including stroke [15–17]. Available data indicate an increased risk of cerebral infarction and intracerebral hemorrhage in patients with CKD (40–46% and 39%, respectively) [18–20]. The factors that increase the incidence of stroke in the course of kidney disease include accelerated atherosclerosis, calcification of the cerebral arteries, hemodynamic disturbances, anemia, and anticoagulation therapy [17,20]. Patients with impaired renal function often develop lobar hemorrhages with extensive damage to brain structures, characterized by a more severe clinical course [21]. Chronic kidney failure worsens the early (the course of the acute stage of stroke), as well as the late prognosis (in terms of mobility and survival), and increases

| Parameter          | Patients with eGFR $\leq 60$ ml/(min×1.73 m$^2$) n=155 | Patients with eGFR $>60$ ml/(min×1.73 m$^2$) n=309 | p (U Mann-Whitney) |
|--------------------|------------------------------------------------------|-----------------------------------------------------|-------------------|
| Age                | 71.1±11.49                                           | 69.75±11.5                                          | 0.66*             |
| Arterial hypertension | 65 (41.9%)                                           | 136 (44.0%)                                        | 0.67              |
| Atrial fibrillation | 42 (27.1%)                                           | 105 (35.0%)                                        | 0.13              |
| Lipid disorders    | 50 (32.3%)                                           | 82 (26.5%)                                         | 0.19              |
| Diabetes           | 64 (41.3%)                                           | 120 (38.8%)                                        | 0.61              |

* t-student’s test; eGFR – estimated glomerular filtration rate.

| Parameter | eGFR $\leq 60$ ml/(min×1.73 m$^2$) n=155 | eGFR $>60$ ml/(min×1.73 m$^2$) n=309 | p (U Mann-Whitney) |
|-----------|------------------------------------------|--------------------------------------|--------------------|
| NIHSS     | 6.85±6.55                                | 5.74±6.12                            | 0.0199             |
| mRankin   | 3.10±1.91                                | 2.43±2.01                            | 0.0005             |

eGFR – estimated glomerular filtration rate; NIHSS – National Institutes of Health Stroke Scale on the 1st day of stroke; mRankin – modified Rankin scale on the 30th day after stroke.
the risk of recurrent stroke [22–26]. CKD was 1 of the 9 most important risk factors for recurrent stroke within 1 year of diagnosis of the previous incident, according to the Fukuoka Stroke Registry Study (FSR) [27]. We found that in the acute stage of stroke, patients with a decreased glomerular filtration rate (eGFR <60 ml/min) have a greater degree of neurological damage. These patients often remain dependent on help for daily activities within 1 month after the stroke. The results obtained allow us to conclude that hyponatremia influences the course of the acute and sub-acute stroke periods. The mean age of onset of stroke and the incidence of other diseases like diabetes, coronary artery disease, and stroke risk factor profiles are different, with men having a higher incidence of coronary artery disease, dyslipidemia, diabetes, carotid stenosis, and tobacco smoking, while women had a higher incidence of atrial fibrillation and hypertension. When compared to men, women were older and more significantly impacted by acute stroke. Some authors demonstrated significantly worse functional outcomes for women compared to men at 1 and 5 years after stroke [28–31]. Other authors have observed that hemorrhagic transformation in acute ischemic stroke and increased mortality during hospitalization were more common in women [32–34].

### Table 3. Clinical state and mortality in female and male according to eGFR (n,%).

| Parameter | eGFR ≤60 ml/min (n,% | eGFR >60 ml/min (n,% | P (Chi²) |
|-----------|----------------------|---------------------|---------|
|           | Female n=64          | Male n=91           |         |
| NIHSS 0–12| 57 (89.1%)           | 65 (71.4%)          | 0.0083  |
| NIHSS >12 | 26 (28.6%)           | 23 (15.3%)          | 0.5900  |
| mRankin 0–3| 35 (54.7%)           | 26 (28.6%)          | 0.1466  |
| mRankin 4–6| 29 (45.3%)           | 44 (29.3%)          | 0.0190  |
| 1 month mortality | 1 (1.6%) | 10 (11.0%) | 0.0244 |

**eGFR** – estimated glomerular filtration rate; **NIHSS** – National Institutes of Health Stroke Scale.

### Table 4. Clinical state, mortality according to serum sodium concentration (mean ±SD).

| Parameter | Na ≤135 mmol/l n=88 | Na >135 mmol/l n=376 | P (U Mann-Whitney) |
|-----------|---------------------|----------------------|--------------------|
| NIHSS     | 8.22±6.58           | 5.62±6.11            | 0.0001             |
| mRankin   | 3.83±1.78           | 2.38±1.96            | 0.0000             |

**NIHSS** – National Institutes of Health Stroke Scale; **mRankin** – modified Rankin scale.

### Table 5. Clinical state, mortality in female i male according to serum sodium concentration.

| Parameter | Na ≤135 mmol/l (n,% | Na >135 mmol/l (n,% | P (test Chi²) |
|-----------|---------------------|---------------------|---------------|
|           | Female n=39         | Male N=49           |         |
| NIHSS 0–12| 32 (82.1%)          | 30 (61.2%)          | 0.0334       |
| NIHSS >12 | 7 (17.9%)           | 19 (38.8%)          | 0.2529       |
| mRankin 0–3| 15 (38.5%)          | 16 (32.7%)          | 0.5710       |
| mRankin 4–6| 24 (61.5%)          | 33 (67.3%)          | 0.0029       |
| 1 month mortality | 2 (5.1%) | 10 (20.4%) | 0.0380 |

**NIHSS** – National Institutes of Health Stroke Scale; **mRankin** – modified Rankin scale.
in patients with CKD [32]. Hirano et al. demonstrated that patients with renal impairment receive less benefit from thrombolytic therapy in the acute stage of stroke [33]. In addition, the same authors demonstrated a higher incidence of iatrogenic bleeding into intracranial structures, causing a high degree of post-stroke morbidity and increased mortality in this group of patients. It has also been demonstrated that chronic kidney disease has a negative effect on the course of other cardiovascular diseases, including coronary heart disease, and a worse prognosis after angioplasty [34–42]. Patients with chronic kidney disease have a higher incidence of occult stroke and microhemorrhages, regardless of incidents of acute cerebral ischemia [16,17]. Imaging studies in patients on hemodialysis (conducted both pre and post mortem) demonstrate the presence of small-vessel infarcts and cerebral atrophy [16,41].

Hyponatremia is another factor that may affect the course and prognosis of patients after stroke. It is the most common electrolyte disorder in hospitalized patients in various clinical settings [42]. Even a small reduction in the serum sodium level is associated with a worse prognosis, regardless of the disease. These observations have also been made in patients with myocardial infarction, pulmonary hypertension, and subarachnoid hemorrhage [43,44]. Additionally, Wannamethee et al. recognized hyponatremia as a potential risk factor for stroke [45]. The relationship between hyponatremia and clinical outcomes after stroke is not completely understood. The worse outcomes in patients with hyponatremia may possibly be explained by osmotic changes (decreased plasma osmolality) resulting in cerebral edema and secondarily increased intracranial pressure. Osmotic changes within neurons could also be responsible for cellular damage and their premature death. In the present study, hyponatremia was associated with a more severe condition of the patients in the acute and subacute phases of their first-ever stroke and a higher incidence of mortality within 1 month of the onset of their first-ever stroke. Therefore, hyponatremia observed in patients with their first-ever stroke could be regarded as an essential risk factor for increased mortality and worse prognosis. Interestingly, in the present study, the effect of hyponatremia on both neurological condition during the first 24 h after stroke and increased mortality rate was significantly higher in men. Other authors obtained similar results. Rodriguez et al. found hyponatremia to be an independent predictor of long-term cumulative mortality rates at 3 and 12 months after stroke and a worse condition at discharge from hospital. It is important to note that no difference has been found when comparing stroke etiologies (ischemic vs. hemorrhagic) in patients with hyponatremia [46]. Huang et al. demonstrated that decreased sodium level (<135 mmol/l) was a predictor of 3-year mortality in patients with their first-ever acute stroke, independent of other clinical predictors of adverse outcome [47]. This study is one of the few that evaluated the effect of kidney function and sodium disturbances on the course and clinical outcomes in patients after their first-ever stroke during short-term observation. It is not known whether adequate correction of sodium level in patients with acute stroke will improve prognosis and reduce the risk of death. It would be interesting to discover why men with impaired renal function had a more unfavorable course of stroke and higher post-stroke mortality. These findings require further investigation.

Conclusions

Renal impairment and hyponatremia are associated with worse neurological condition in patients in the acute stage of their first-ever stroke and worse outcomes within 1 month after a neurological event. Male patients with impaired kidney function and hyponatremia have a more severe course of a first-ever stroke and greater short-term mortality compared to females.
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