Ann. Acad. Med. Siles. (online) 2016; 70: 127–132
eISSN 1734-025X
DOI:10.18794/aams/62375

PRACA ORYGINALNA
ORIGINAL PAPER

Prognostic relevance of hyponatremia after first-ever ischemic stroke

Znaczenie hiponatremii u chorych z pierwszym w życiu udarem niedokrwiennym mózgu

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ABSTRACT

INTRODUCTION: Hyponatremia is examined as a prognostic factor after first-time ischemic cerebrovascular incident (CVA, ischemic stroke).

MATERIALS AND METHODS: 677 patients were analyzed after first-time ischemic stroke and divided into two groups according to sodium concentration: ≤ 135 mmol/L and > 135 mmol/L.

RESULTS: For patients with sodium levels ≤ 135 mmol/L, the median National Institutes of Health Stroke Scale (NIHSS) score was 5 points, the median Modified Rankin Scale (mRS) was 4 points, and the mortality within 1 month of ischemic stroke was 10.5%. Patients with sodium levels > 135 mmol/L: NIHSS 3 points, mRS 2 points and mortality 1 month after ischemic stroke 3.4%. Mortality within 1 month of ischemic stroke in hyponatremic patients: women 16.4%, men 3.5% (p = 0.0194). Greater disability was seen in eunatremic women as assessed by increased mRS scores (p = 0.005).

CONCLUSIONS: Hyponatremia is associated with a worsened heath status in patients in the acute and sub-acute phase after first-time ischemic stroke and is associated with increased mortality within 1 month after the stroke. Women with hyponatremia were characterized by greater mortality within one month after their first-ever ischemic stroke. In women with normal serum sodium at the time of stroke, a higher degree of disability was observed as assessed by increased mRS scores compared to men.

KEY WORDS
stroke, risk factors, hyponatremia, prognosis

Received: 27.01.2016 **Revised:** 25.03.2016 **Accepted:** 25.03.2016 **Published online:** 21.07.2016

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STRESZCZENIE

WSTĘP: Hiponatremię uważa się za czynnik ryzyka udaru mózgu.
MATERIAŁ I METODY: Przeanalizowano 677 chorych z pierwszym w życiu udarem niedokrwiennym mózgu, których podzielono w zależności od stężenia sodu w surowicy na dwie podgrupy: ≤ 135 mmol/l i > 135 mmol/l.
WYNIKI: U chorych ze stężeniem sodu ≤ 135 mmol/l mediana w skali NIHSS wyniosła 5 pkt, mediana oceny stopnia inwalidztwa według skali mRankin wynosiła 4 pkt, a śmiertelność w okresie jednego miesiąca od zachorowania wynosiła 10,5%, w grupie ze stężeniem sodu > 135 mmol/l stwierdzono odpowiednio: 3 pkt, 2 pkt, i 3,4%. U chorych z hiponatremią śmiertelność w ciągu miesiąca od zachorowania wynosiła u kobiet 16,4%, u mężczyzn 3,5% (p = 0,0194). U kobiet z prawidłową natremią obserwowano większy stopień inwalidztwa w skali mRankin (p = 0,005).
WNIOSKI: Hiponatremia ma niekorzystny wpływ na stan pacjentów zarówno w ostrej, jak i podostrej fazie udaru oraz wiąże się ze zwiększoną śmiertelnością miesięczną od zachorowania. Kobiety z hiponatremią cechowała większa śmiertelność w ciągu jednego miesiąca po przebytym pierwszym w życiu udarze niedokrwiennym. U kobiet z prawidłowym stężeniem sodu w czasie pierwszego w życiu udaru niedokrwiennego stwierdzano wyższy stopień inwalidztwa ocenianego w skali mRankin w porównaniu z mężczyznami.

SŁOWA KLUCZOWE
udar, czynniki ryzyka, hiponatremia, rokowanie

INTRODUCTION

Since hyponatremia is considered an important risk factor for stroke [11,12,13], we evaluated the relationship between serum sodium levels and the prognosis of patients after their first-time ischemic stroke.

Ischemic stroke is defined as brain ischemia by reason of any pathologic process that limits blood supply to the brain and results in acute neurological injury. Clinically, ischemic stroke is characterized by rapidly progressing focal or generalized symptoms of declining brain function lasting more than 24 hours or leading to death [1]. Stroke is the third most common cause of death in developed countries (after heart disease and cancer) and the leading cause of disability in adults. The annual incidence of stroke in the general population (Poland) is estimated at 0.2% [2].

Hyponatremia (serum sodium ≤ 135 mmol/L) is the most common electrolyte imbalance in hospitalized patients [3,4] and is seen in approximately 28% of patients admitted to hospital (approx. 15–20% emergency hospital admissions), 21% of patients in the ER and 7.2% of outpatients [5,6]. Hyponatremia is associated with increased mortality, morbidity and increased hospitalization time. Even a small reduction in serum sodium is associated with a worse prognosis, regardless of the etiology [7]. Hyponatremia is also a common electrolyte disorder seen in patients with subarachnoid hemorrhage [8,9,10].

MATERIALS AND METHODS

Our study group consisted of 677 patients, 355 women with a mean age of 70.6 years and 322 men with a mean age of 69.8 years. The youngest study participant was 28 years old and the oldest 92 years old. The study group characteristics are presented in Table I. The patients were treated at the Department of Neurology, Medical University of Silesia Hospital No. 7, Professor Leszek Giec Upper Silesian Medical Centre in Katowice between the years 2012 and 2015 after first-ever ischemic stroke – diagnosed according to WHO criteria and confirmed with head CT or MRI. Patients with transient ischemic attack (TIA), acute intracranial hemorrhage complicated by ischemic stroke in the course of vasospasm and patients with end-stage renal disease (eGFR < 15 ml/min) were not included in the study group.

The following data was collected for all the patients enrolled in the study:

– age (at diagnosis of first ischemic stroke);
– medical history and blood tests carried out in the last year;
– medication history prior to admission;
– comorbidities such as hypertension, atrial fibrillation, diabetes and lipid abnormalities;
– neurological condition on day 1 of stroke as assessed by NIHSS (National Institutes of Health Stroke Scale); NIHSS is used to assess and qualify

Table I. Study group characteristics
Tabela I. Charakterystyka grupy badanej

	Women (1) n = 355	**Men (0) n = 322**	**p**
Age (years)	70.6 ± 11.0 median 72 min 28, max 92	69.8 ± 12.0 median 71 min 28, max 92	0.3669
Comorbidities:			
Hypertension (n,%)	193 (54.4%)	192 (59.6%)	0.1675
Atrial fibrillation (n,%)	105 (29.6%)	97 (30.1%)	0.8766
Lipid disorders (n,%)	103 (29.0%)	87 (27.0%)	0.5639
Type 2 diabetes (n,%)	136 (38.3%)	113 (35.1%)	0.3861
Chronic kidney disease:			
eGFR ≤ 60 ml/(min × 1,72 m²)	132 (37.2%)	89 (27.6%)	0.0082
eGFR > 60 ml/(min × 1,72 m²)	223 (62.8%)	233 (72.4%)	0.0082
Ischemic stroke location:			
Left hemisphere (n,%)	129 (36.3%)	129 (40.1%)	0.3191
Right hemisphere (n,%)	77 (21.7%)	64 (19.9%)	0.5615
Brain stem (n,%)	128 (36.1%)	108 (33.5%)	0.4927
Multifocal (n,%)	14 (3.9%)	15 (4.7%)	0.6465
Cerebellum (n,%)	7 (2.0%)	6 (1.9%)	0.9182
Anti-platelet medication:			
Aspirin (n,%)	151 (42.5%)	152 (47.2%)	0.2224
Clopidogrel (n,%)	11 (3.1%)	13 (4.0%)	0.5095
Anti-coagulant medication:			
Acenocoumarol (n,%)	27 (7.6%)	19 (5.9%)	0.3787
Warfarin (n,%)	28 (7.9%)	29 (9.0%)	0.6006
Antihypertensive drugs:			
B-blockers (n,%)	91 (25.6%)	88 (27.3%)	0.6174
Diuretics (n,%)	45 (12.7%)	29 (9.0%)	0.1264
Calcium channel blockers (n,%)	25 (7.0%)	12 (3.7%)	0.0580
ACE-I (n,%)	59 (16.6%)	70 (21.7%)	0.0903
Alfa-1-blockers (n,%)	4 (1.1%)	6 (1.9%)	0.4275
Angiotensin receptor blockers (n,%)	15 (4.2%)	10 (3.1%)	0.4404
Diabetes medication:			
Insulin (n,%)	68 (19.2%)	58 (18.0%)	0.7029
Oral hypoglycemic drugs (n,%)	61 (17.2%)	45 (14.0%)	0.2514
Hypolipidemic agents:			
Statins (n,%)	104 (29.3%)	91 (28.3%)	0.7665
Fibrates (n,%)	14 (3.9%)	3 (0.9%)	0.0124
Thrombolytic treatment (n,%)	35 (9.9%)	31 (9.6%)	0.9191

patients for thrombolytic therapy, neurosurgical or endovascular surgery and subsequent patient care;
– type of therapy: thrombolytic or antiplatelet therapy;
– mortality within 1 month after stroke;
– functional status on day 30 according to mRS (a 6-point disability scale) – assessed by telephone with the patient's family.

Data was also analyzed according to patient gender.
Hypertension was assessed according to the diagnostic criteria of the Polish Cardiac Society (2013) [16]. Diabetes was diagnosed according to the criteria the Polish Diabetes Society (2014) [17]. Abnormal total cholesterol was defined at > 200 mg/dl (> 5.18 mmol/L), LDL cholesterol > 100 mg/dl (2.5 mmol/L), HDL cholesterol < 35 mg/dl (0.91 mmol/L) or triglycerides > 135 mg/dL (1.53 mmol/L). Atrial fibrillation was identified based on patient history or diagnosed during hospitalization (ECG, 24-hour ECG).
Ethical committee approval was not required because the study was based on routine laboratory tests performed in every patient with a stroke – no patient identification was recorded and thus the study did not fulfill the criterion of a medical experiment (Commission Decision Bioethics SUM CDF/0022/MB/210/14).

Laboratory tests

All the assays were routine, performed on the day of admission for each hospitalized patient with ischemic stroke. Patient information was not shared beyond the physicians and researchers involved in the study. The patients were analyzed for:
– serum sodium (Na) and creatinine,
– estimated glomerular filtration rate (eGFR) (obtained by CKD-EPI) [18].

Our study group was divided according to serum sodium levels:
1. Serum sodium ≤ 135 mmol/L
2. Serum sodium > 135 mmol/L

Statistical Analysis

Statistical analysis was performed using Statistica PL 8.0. The data are presented as both the mean with standard deviation and median value. The distribution was analyzed using the Kolmogorov-Smirnoff test. The Mann-Whitney U test was used to compare the study groups and for age we used the *t* test. Parameter changes over time were assessed by ANOVA. $p < 0.05$ was considered statistically significant. Correlation coefficients (R) were calculated by Spearman's rank correlation.

RESULTS

In patients with serum sodium < 135 mmol/L, we observed:
– a worse neurological status in acute stroke (median NIHSS scale was 5 points, in patients with Na > 135 mmol/L, 3 points);
– a worse neurological status in the sub-acute phase of stroke – median mRS score was 4 points (in patients with Na > 135 mmol/L the median mRS score was 2 points);
– higher mortality within 1 month after ischemic stroke (results are shown in Table II).

We observed that women with hyponatremia are at increased risk of death within a month after ischemic stroke as compared to men (16.4% vs. 3.5%, $p = 0.0194$).
Eunatremic women were at risk of a greater degree of disability after ischemic stroke as assessed by mRS and compared to men ($p = 0.005$).
Hyponatremia had no effect on the neurological condition of female patients in the acute and subacute phase after ischemic stroke (results are shown in Table III).

Table II. Clinical condition, functional status and mortality within 1 month after stroke depending on serum sodium concentration
Tabela II. Stan kliniczny, funkcjonalny oraz śmiertelność w okresie 1. miesiąca po wystąpieniu udaru w zależności od stężenia sodu w surowicy

Parameter	Na ≤ 135 mmol/l n = 124	Na > 135 mmol/l n = 553	p
NIHSS	**7.4 ± 6.3** **median 5.0** **min 0, max 29**	5.2 ± 5.6 median 3.0 min 0, max 29	0.0000
mRS	**3.6 ± 1.8** **median 4.0** **min 0, max 6**	2.3 ± 1.9 median 2.0 min 0, max 6	0.0000
Mortality within 1 month	**13 (10.5%)**	19 (3.4%)	0.0008

Mortality compared with Chi^2 statistic

Table III. Patient clinical status, functional status and mortality within 1st month after ischemic stroke as related to serum sodium levels in men and women
Tabela III. Stan kliniczny, funkcjonalny oraz śmiertelność w okresie 1. miesiąca po wystąpieniu udaru w zależności od stężenia sodu w surowicy badanych mężczyzn i kobiet

Parameter	Na ≤ 135 mmol/l (n,%)			Na > 135 mmol/l (n,%)		
	Women (1) n = 67	Men (0) n = 57	p (Chi²)	Women (1) n = 288	Men (0) n = 265	p (Chi²)
NIHSS						
0–12	46 (68.7%)	46 (80.7%)	0.1266	246 (85.4%)	237 (89.4%)	0.1558
> 12	21 (31.3%)	11 (19.3%)		42 (14.6%)	28 (10.6%)	
mRS						
0–3	27 (40.3%)	23 (40.4%)	0.9953	**179 (62.2%)**	**194 (73.2%)**	**0.0056**
4–6	40 (59.7%)	34 (59.6%)		**109 (37.8%)**	**71 (26.8%)**	
Mortality within 1 month	**11 (16.4%)**	**2 (3.5%)**	**0.0194**	12 (4.2%)	7 (2.6%)	0.3253

NIHSS – National Institute of Health Stroke Scale; mRS – modified Rankin Scale
NIHSS and mRS compared with Mann-Whitney U test

Mortality compared with Chi² statistic.

DISCUSSION

Our study suggests that hyponatremia is associated with a worse prognosis, increased disability and greater mortality of patients in the acute and subacute phase following first-time ischemic stroke. Thus, in patients hospitalized for first-time ischemic stroke, hyponatremia is a potential risk factor for a negative clinical course, both as to increased mortality and progression of underlying disease. The mechanism of this association remains unclear. One possible explanation is that severe ischemic stroke in patients with hyponatremia results in a reduction in plasma osmolality which secondarily may increase the risk of brain edema and increased intracranial pressure. A nerve cell osmolarity imbalance leads to cell damage or death. Rodriguez et al. [14] recognized hyponatremia as an independent factor associated with increased mortality after 3 to 12 months after ischemic stroke and poor health status at hospital discharge. These observations were not influenced by the stroke etiology (ischemic vs. hemorrhagic). It was demonstrated by Huang et al. [15] that reduced serum sodium concentration (< 135 mmol/L) is associated with increased mortality after first ischemic stroke during a 3-year follow-up, regardless of other risk factors for vascular incidents. Interestingly, no association with hyponatremia or increased mortality in the early period after ischemic stroke was found (during hospitalization and 1 to 3 months post discharge).

The etiology of hyponatremia in patients with ischemic stroke includes a low sodium diet (treatment of hypertension), diuretics and infection (primarily aspiration pneumonia) [16]. Hyponatremia in post ischemic stroke patients is most commonly hypoosmolal, due to the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting syndrome (CSWS) [8].

We observed an association between women after ischemic stroke with hyponatremia and poor long-term prognosis. Women with hyponatremia were characterized by higher mortality within a month after ischemic stroke as compared to men. In addition, eunatremic women attained higher mRS disability scores as compared to men. Similar relationships were described by JMRamirez-Moreno and colleagues [17], who also observed a more severe decline in the quality of life for women after ischemic stroke than men. In contrast, Roquer J. et al. [18] showed that women have different cardiovascular risk profiles and distributions of ischemic stroke sub-types as compared to men. Hypertension and cardiac embolisms were independent factors associated with the female gender. Alcohol abuse, smoking, and small vessel disease were associated with the male sex. Clinically, women were more likely to manifest aphasia, impaired vision and dysphagia than men. Women were more frequently affected by emboli of cardiac origin. Men were more often affected by atherosclerosis induced stroke and lacunar strokes. In addition, the hospitalization of women with ischemic stroke was longer than the duration of hospitalization for men. The reason for these male and female prognostic inconsistencies remains unclear and requires further study.

Our study is one of only a few in Poland that considers serum sodium and its impact on the prognosis, disability and mortality after ischemic stroke. An additional advantage of this study is the large

sample size. Our paper is limited by the retrospective approach of this study, which makes data analysis difficult. While the negative impact of gender on the study parameters is obvious and well documented, it is not clear which factors affect the worse female prognosis. It is also remains unclear whether correcting serum sodium levels in patients in the acute phase of ischemic stroke improves prognosis, reduces mortality and disability post ischemic stroke. Finally, does modification or adjustment of prescribed medication improve the prognosis in patients with ischemic stroke?

CONCLUSIONS

1. Hyponatremia has a negative impact on the health status of patients in the acute and sub-acute phase after stroke and is associated with an increased 1 month mortality.
2. Women with hyponatremia are characterized by greater mortality within one month after first-ever ischemic stroke.
3. In women with normal serum sodium at the time of their first ischemic stroke, there was a higher degree of disability (mRS) as compared to men.

Author's contribution:

Study designe – A. Lasek-Bal, M. Holecki, J. Duława
Data collection – B. Kret
Data interpretation – A. Lasek-Bal, M. Holecki, B. Kret, A. Hawrot-Kawecka,
Statistical analysis – A. Lasek-Bal, M. Holecki, B. Kret, A. Hawrot-Kawecka, J. Duława
Manuscript preparation – B. Kret, A. Lasek-Bal, M. Holecki, A. Hawrot-Kawecka, K. Wilczyński
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