THE RELATIONSHIP BETWEEN DIAGNOSIS AND SEVERITY OF ISCHEMIC STROKE AND SERUM UROTENSIN-II LEVELS

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ABSTRACT

Introduction: Urotensin-II is an extremely potent, widespread vasopressor and increased serum urotensin-II level is associated to many disorders including congestive heart failure, hypertension, coronary artery diseases, diabetes mellitus and metabolic syndromes. In this study we aimed to investigate whether there is a relationship between serum urotensin-II level and etiology and severity of stroke in patients with ischemic cerebrovascular disease.

Materials and methods: The study included 20 patients experienced acute ischemic cerebrovascular event (study group) and 20 healthy individuals (control group). Venous blood samples were drawn from patients who experienced acute ischemic stroke within prior 12 hours and urotensin-II measurements were performed by ELISA kits using sandwich enzyme-linked sorbent immunoassay method.

Results: No significant difference was observed in serum urotensin-II levels between study and control groups. In the analysis of ischemic stroke subgroups, urotensin-II level was found to be significantly higher in patients with cardioembolic stroke. In addition, a positive correlation was detected between urotensin-II level and high National Institutes of Health Stroke Scale (NIHSS) score at presentation.

Conclusion: This is the first study analysing urotensin-II levels in stroke, concluding that urotensin-II could be a relevant parameter for assessment of etiology and severity of stroke.

Keywords: urotensin-II, ischemic stroke, severity, cardioembolic stroke.

DOI: 10.19193/0393-6384_2018_2_54

Received August 30, 2017; Accepted January 20, 2018

Introduction

Stroke is the most common cause of morbidity and the third most common cause of mortality in adults. While stroke patients die 30% in the first year, 30% of those who live in need daily help in their daily work. The most common stroke type of is ischemic nature, which is seen in about 85%. Most of the risk factors that lead to stroke are modifiable risk factors16. In the treatment of ischemic stroke, appropriate thrombolytic therapy can be given in the first 4,5 hours while mechanical thrombectomy can be performed in the first 6 hours in case of large vessel occlusion5.

Urotensin-II (U-II) is a cyclic peptide which was first isolated from neurosecretory system of goby fish3. The U-II and its receptors are mostly found at peripheral vascular tissues, heart and kidneys, although they are also present in central nervous system (CNS) and other tissues4. The U-II play role in potent hemodynamic events, positive inotropic and chronotropic responses, osmoregulation, induction of collagen and fibrin deposition, modulation of inflammatory response and cardiac
and vascular hypertrophy. It also causes a potent angiogenic activity\(^5,6\).

The U-II is an extremely potent, widespread vasopressor with increased serum levels in several disorders including congestive heart failure, hypertension, coronary artery diseases, diabetes mellitus and metabolic syndrome. In previous studies, it was demonstrated that the U-II is one of the most potent vasoconstrictors in mammals and that it may have an important role in regulation of cardiovascular homeostasis\(^7\).

The U-II distribution varies among species. The U-II encoding structures in CNS are mainly located at motor neurons of brainstem and spinal cords. The U-II is also secreted by cortex and cerebellum\(^8\). Ischemic stroke has subtypes such as large vessel atherosclerosis, small vessel atherosclerosis and cardioembolic. They can develop with different mechanisms\(^9\). U-II levels may increase in cardiovascular diseases\(^7\). Probably the same relationship be valid in ischemic stroke.

In this study, we investigated serum U-II levels and potential relationship between U-II and stroke etiology and other disease parameters.

**Materials and methods**

**Study design, patient selection and data collection**

The study was approved by Ethics Committee of Ankara education and research hospital. The study included 20 patients experienced acute ischemic cerebrovascular accident and 20 healthy individuals as controls.

In all cases, age, gender, medical history, localization of ischemic region on diffusion-weighted magnetic resonance imaging (DWI-MRI) and stroke severity score [National Institutes of Health Stroke Scale (NIHSS)] were recorded. To identify etiology, trial of ORG 10172 in acute stroke treatment (TOAST) classification was used in all patients. The patients with chronic renal failure (serum creatinine >2.0 mg/dL), uncontrolled diabetes mellitus (HbA1c >8), uncontrolled hypertension, coronary artery disease, familial dyslipidemia, systolic cardiac failure (ejection fracture <45%), cardiomyopathy or liver failure were excluded. All participants gave informed written consent form.

**Laboratory parameters**

Venous blood samples were drawn from patients who experienced acute ischemic stroke within prior 12 hours. The blood samples were centrifuged at 1000 rpm for 15 minutes. Sera obtained were stored at -80°C until assays. The U-II measurement was performed by Human Urotensin-II ELISA kits (Shanghai Yehua Biological Technology) in Elx 50 Auto Strip Washer (BIO-TEK Instruments Inc., USA) and ELX 800 Micro-Plate Reader (BIO-TEK Instruments Inc., USA) using Sandwich Enzyme-Linked Sorbent Immunoassay technique. The kit sensitivity was 2.23 ng/mL.

**Statistical Analysis**

All analyses were performed using Statistical Package for the Social Sciences for version 11.5. The independent samples t test was used to compare continuous variables with normal distribution while Mann Whitney test was used to compare continuous variables with skewed distribution. The Spearman rank correlation analysis was used to assess correlation between continuous variables and U-II. The Wilcoxon match pair test was used to compare NIHSS scores at presentation and on the month 3. p value <0.05 was considered as statistically significant.

**Results**

No significant difference was observed in serum U-II levels between study and control groups (p=0.804 and p=0.344, respectively; Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Control (n=20)</th>
<th>Study (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>65.80±12.44</td>
<td>64.90±10.21</td>
<td>0.804</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6(%30.0)</td>
<td>14(%70.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Female</td>
<td>14(%70.0)</td>
<td>6(%30.0)</td>
<td></td>
</tr>
<tr>
<td>Urotensin-II (mean ± SD)</td>
<td>149.13±176.71(106.21)</td>
<td>194.18±188.63(137.81)</td>
<td>0.344</td>
</tr>
</tbody>
</table>

Table 1: The age, gender and urotensin-II levels in the study and control groups.

When ischemic stroke etiology was identified, according to TOAST classification, it was found that there was atherosclerotic great vessel disease in 70%, cardioembolic stroke in 25% and lacunar stroke in 5%. The NIHSS score at presentation was found to be 9.70 ± 5.75 (9.50).

When relationship between U-II and ischemic stroke subgroups was analyzed, urotensin-II level
was found to be significantly higher in patients with cardioembolic stroke (p=0.02; Figure 1). No correlation was found between U-II levels and other risk factors (Table 2).

### Table 2: The urotensin-II levels according to etiological factors.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Urotensin-II Mean ± SD (median)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>158.58±127.14 (130.80)</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>327.91±287.14 (210.00)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>206.81±183.91 (135.65)</td>
<td>0.967</td>
</tr>
<tr>
<td>Positive</td>
<td>188.77±197.20 (140.82)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>183.13±190.88 (139.61)</td>
<td>0.727</td>
</tr>
<tr>
<td>Positive</td>
<td>227.35±199.14 (132.67)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>212.54±216.38 (134.84)</td>
<td>0.694</td>
</tr>
<tr>
<td>Smoker</td>
<td>139.10±9.01 (140.60)</td>
<td></td>
</tr>
</tbody>
</table>

**Fig 1**: The correlation between serum urotensin-II level and stroke etiology.

A significant elevation was detected in U-II levels by increasing NIHSS scores at presentation, a marker for severity of stroke (p=0.001; Table 3).

A significant correlation was detected between U-II levels and NIHSS changes from presentation to month 3 (p=0.037; Figure 2).

### Table 3: The relationship between urotensin-II level and NIHSS score changes from presentation to month 3.

<table>
<thead>
<tr>
<th>NIHSS at presentation</th>
<th>NIHSS on the month 3</th>
<th>NIHSS difference</th>
<th>Urotensin</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>-0.113</td>
<td>0.636</td>
<td>-0.37</td>
</tr>
<tr>
<td>Modified Rankin score</td>
<td>0.003</td>
<td>0.005</td>
<td>0.418</td>
</tr>
<tr>
<td>NIHSS at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS on the month 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS difference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig 2**: The correlation between serum urotensin-II level and changes in NIHSS score

### Discussion

Acute ischemic stroke remains to be an important cause of mortality and morbidity despite advances in the treatment of disease. Cardioembolic strokes account for approximately 14-30% of all ischemic strokes, which have high mortality and recurrence at long-term; thus, cardiac etiologies resulting in stroke at both acute and chronic period should be fully understood. We believe that a diagnostic serum marker such as U-II will provide important clinical benefits in the diagnosis, etiology and prognosis of acute ischemic stroke.

The plasma U-II levels show positive correlation with several disorders such as congestive heart failure, primary hypertension, coronary artery disease, diabetes mellitus and metabolic syndrome. Again, it was shown that plasma U-II levels are elevated in chronic renal failure, cirrhosis and portal hypertension. In addition, recent evidence showed that U-II is a useful biomarker in patients with diabetic retinopathy, type II diabetes mellitus with atherosclerosis and rheumatoid valve diseases.

The U-II is an extremely potent, widespread vasopressor. The U-II levels are associated to many cardiovascular disorders including congestive heart
failure, hypertension, coronary artery disease, diabetes mellitus and metabolic syndrome\textsuperscript{11}. In our study, U-II levels were found to be significantly higher in patients which experienced cardioembolic stroke when compared to other subgroups when assessed according to etiology of stroke. The finding of increased U-II levels in cardioembolic strokes cases compared to other types of stroke could be due to underlying cardiac disorder. However, positive correlation between increased NIHSS score and elevated serum U-II levels suggests that cerebral lesion might also be associated.

The U-II is mainly secreted by heart, brain, endothelial cells and vascular smooth muscle cells, existing in plasma circulation. It is most potent vasoconstrictor in mammalian and can contribute to cardiovascular disorders by involving in hypertension and atherosclerotic processes\textsuperscript{12,13}.

It has been proven that U-II levels are increased in the presence of atherosclerotic carotid artery disease and aortic plaques. It has been proposed that this secretion results in proliferation of vascular smooth muscles and atherosclerotic plaque formation\textsuperscript{14}.

Animal studies showed that nitric oxide and prostaglandin secretion is increased by stimulation of U-II receptor of endothelial cells. However, effects of these vasodilators can be directly neutralized by vasoconstrictor activity of U-II\textsuperscript{15}. The correlation between high NIHSS scores and serum U-II levels suggests that U-II receptors may have role in occurring and progression of cerebral injury following ischemic stroke.

The presence of U-II receptors in cerebral areas (including olfactory region, bulb, hippocampus, hypothalamus, thalamus, epiphysis, tegmentum, tectum, pituitary gland, pons, bulbus and spinal cord)\textsuperscript{16}, role of U-II in vascular, hormonal, inflammatory and oxidative systems and higher serum U-II levels in the group with higher NIHSS scores suggest that U-II may play role in disease physiopathology.

To best of our knowledge, this is the first study investigating the association between stroke and serum U-II levels. To best of our knowledge, there is no such study in the literature. The U-II was found to be relevant in identifying etiology and prognosis of stroke but further studies are needed due to limited study population and follow-up in our study.

References

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