LIPOPROTEINURIA AS AN INDEPENDENT PREDICTOR OF UNFAVORABLE OUTCOME AFTER INTRAVENOUS THROMBOLYSIS IN ISCHAEMIC STROKE

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Abstract

Patients with proteinuria and declined glomerular filtration rate (GFR) are at high risk of developing stroke. Purpose of this study was to review and analyze available literature to identify role of proteinuria along with decreased GFR as one of the predictors of unfavorable outcome of ischaemic stroke in patients receiving intravenous thrombolysis therapy in routine clinical practice. Proteinuria is an independent predictor of negative outcome after intravenous thrombolysis treatment in ischaemic stroke, which demonstrates significant impact of chronic kidney disorders in effectiveness of thrombolytic therapy.

Keywords: ischaemic stroke, cerebrenal disfunction, proteinuria, glomerular filtration rate, intravenous thrombolysis, hemorrhagic transformation.

Introduction: Chronic kidney disease (CKD) is an important health/social problem worldwide [4,5,17,21,47]. CKD patients are at higher risk for developing cardiovascular and cerebrovascular diseases, including ischaemic stroke (IS) in comparison with individuals who do not have CKD [3,5,23,27]. It is known that presence of kidney disorders in patients with cardiovascular diseases is a predictor for unfavorable disease outcome. Proteinuria and declined glomerular filtration rate (GFR) are considered markers for negative outcome cardiovascular practice [4,5,27]. Kidney disorders are also accompanied by high mortality rate and unfavorable clinical outcome in stroke [31,48]. Currently, intravenous systemic thrombolysis therapy remains as one of the most effective routine treatment for acute IS [6,42,45,46]. However, impact of CKD on outcome of stroke and hemorrhagic complications after thrombolytic therapy has not been established.

Research data shows that, increased level of serum creatinine or decreased GFR act as predictors of unfavorable clinical outcome at three months following intravenous thrombolytic therapy in IS cases [29,32], whereas a number of researchers have been unable to identify association between $GFR < 60 \text{ ml/min/m}^2$ and negative outcome or death [11]. On the other hand, pro-

teinuria, as a marker of CKD is considered an independent risk factor for development of stroke and negative disease outcome [10,17,27,28,31,33,40,48]. Studies have demonstrated that presence of albuminuria after thrombolysis may act as a predictor of hemorrhagic transformation in acute IS patients [16].

In their research, Chen C.H. et al. (2013) demonstrated that in acute IS patients, proteinuria was associated with unfavorable disease outcome at three months after administration of intravenous thrombolytic therapy and this effect was dependent on age (elderly), gender (male), degree of severity of IS, and co-morbid conditions at a statistically significant rate. In addition, negative impact of thrombolysis increased proportionally to the level of proteinuria. Unlike proteinuria, it was determined that contribution of decreased GFR, measured by level of serum creatinine upon admission, to unfavorable clinical outcome or hemorrhagic complications is statistically insignificant, even at the rate of $GFR < 45 \text{ ml/min/m}^2$ [15].

Based on previously published data, factors such as elderly age, high NIHSS scores upon admission, recent stroke as evidenced by neuroimaging results, high blood pressure, or pre-morbid functional deficiency are associated with unfavorable disease outcome following adminis-

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tration of rt-PA [38,39,42,44]. However, cerebrorenal disfunction is infrequently mentioned in these studies. Theoretically, CKD patients have coagulation and thrombocytic function disorders, which lead to thrombosis if inadequately treated; however, hemorrhagic complications occur after use of anti-thrombocytic and anti-coagulant agents [21]. Although, CKD is not listed as a contraindication for intravenous administration of rt-PA in multiple clinical trials and guidelines [23,24,34], it is still unclear as to whether CKD patients may achieve relatively satisfactory outcome after intravenous thrombolytic agent administration or they will develop hemorrhagic complications in any case, compared to non-CKD patients.

A Swedish research with participation of 196 IS patients receiving rt-PA, has shown that high level of serum creatinine upon admission to healthcare facility is an independent predictor of unfavorable outcome ($mRS \geq 3$) after three months [29]. Based on the data from multi-center stroke registry in Japan, which included 578 patients receiving rt-PA, level of $GFR < 60$ ml/min/m² is an independent predictor of hemorrhagic complications, unfavorable clinical outcome after 3 months, and death [32]. However, results of a study conducted in American Stroke Center with the participation of 74 patients, who received rt-PA treatment demonstrated that, level of $GFR < 60$ ml/min/m² is not associated with high risk of hemorrhagic complications, unfavorable clinical outcome after 3 months, and death [11].

Based on the results of large population studies, risk of cardiovascular diseases and death increases dramatically in patients with $GFR < 45$ ml/min/m² [22], although a number of other studies were unable to establish statistically significant relation with unfavorable outcome in IS [15].

Proteinuria is used as an indicator for screening for CKD [10,13]. It is a symptom of chronic damage in glomerular barrier and often precedes noticeable decline in renal filtration [10]. Proteinuria itself increases risk of stroke by approximately 50-70% [33,48]. Based on data from large stroke registry in Japan, proteinuria

leads to deterioration of neurologic deficiency, unfavorable outcome, and high mortality in acute IS patients [27]. A Korean single-center study has shown that, presence of micro- and macroalbuminuria following intravenous treatment with thrombolytic agents associates with hemorrhagic transformation (HT), including parenchymal and symptomatic intracerebral hemorrhages [16]. Results of a Taiwanese study reveal that, proteinuria is an independent predictor of unfavorable outcome in patients treated with rt-PA, effectiveness of which correlates with degree of severity of proteinuria [14,15].

Precise mechanism of association between proteinuria and unfavorable prognosis after administration of rt-PA in IS patients has not been established yet. First, presence of albuminuria is a predictor of HT in site of ischaemia, including in patients who receive intravenous thrombolytic agents [16,37].

One of modern approaches to explain involvement of proteinuria (or microalbuminuria) in pathogenesis of unfavorable outcome of IS is through endothelial dysfunction markers [1,18,19,36]. Increased capillary permeability for albumin in systemic circulation may result in systemic hemodynamic changes, which, ultimately, lead to development and progression of atherosclerosis. Besides, albuminuria is closely related to high concentration of von Willebrand factor in serum and other markers of endothelial dysfunction, i.e., it serves as a factor for formation of micro-thrombi [25,35]. Patients with proteinuria usually have more severe neurologic damage at the onset of IS, which may point to more generalized atherosclerotic process at an earlier stage. Consequently, existence of proteinuria may have a relationship with systemic vascular damage and atherosclerotic process [15]. However, whether or not proteinuria affects thrombolytic therapy in vascular recanalization in acute IS patients, has not been yet established and warrants further research. Considering aforementioned, a conclusion may be withdrawn that, proteinuria, along with GFR is an independent predictor of unfavorable outcome after intravenous administration of thrombolytic agents in acute IS cases.

Conclusion. Despite achievements of nephrology, role and functional status of kidneys have been insufficiently studied in cerebrovascular diseases, specifically in stroke cases and there is no unified opinion regarding participation of angio-cerebro-renal disorders in pathogenesis, course, and outcome of stroke. Based on the analysis of available literature, we were able to identify that, proteinuria is one of the most important predictors of functional outcome after three months following thrombolytic therapy in IS patients. Here, contribution of acute vascular catastrophe itself and development of transient proteinuria may not be excluded. Therefore, baseline and follow up urine tests are recommended before stroke and upon occurrence of it, in order to avoid unfavorable clinical outcome. Also, it would be appropriate to evaluate presence of microalbuminuria or albumin/creatinine

ratio in urine samples, which should be considered upon administration of thrombolytic therapy in IS patients.

Co-existence of renal dysfunction and IS presents serious problems in selecting appropriate treatment regimen in patients, who should receive a combination therapy, consisting of neuro- and nephroprotection strategies, taking both co-morbid conditions into account. This allows studying novel pathways of pathogenesis, clinical picture, and outcome of IS with consideration of vascular/cerebral/renal disorders and development of neuro- and nephroprotective treatment approaches. Additional nephroprotective treatment should be in place in patients with proteinuria with the purpose of achieving improvement in proteinuria, which in its turn will increase effectiveness of thrombolytic therapy and clinical outcome in IS cases.

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РЕЗЮМЕ

ЯВЛЯЕТСЯ ЛИ ПРОТЕИНУРИЯ НЕЗАВИСИМЫМ ПРЕДИКТОРОМ НЕБЛАГОПРИЯТНОГО ИСХОДА ПОСЛЕ ВНУТРИВЕННОГО ТРОМБОЛИЗИСА ПРИ ИШЕМИЧЕСКОМ ИНСУЛЬТЕ?

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Больные с протеинурией и сниженной скоростью клубочковой фильтрации имеют высокий риск развития инсульта. Целью настоящего исследования является анализ доступной литературы для изучения роли протеинурии, кроме сниженной величины скорости клубочковой фильтрации, как одного из предикторов неблагоприятного исхода ишемического инсульта у больных, получавших внутривенный тромболитический препарат в рутинной клинической практике. Протеинурия является независимым предиктором неблагоприятного исхода после внутривенного тромболитического препарата при ишемическом инсульте, свидетельствующим о значительном влиянии хронической болезни почек на эффективность тромболитической терапии.

Ключевые слова: ишемический инсульт, церебро-ренальная дисфункция, протеинурия, скорость клубочковой фильтрации, внутривенный тромболитический препарат, геморрагическая трансформация.

XÜLASƏ

PROTEİNURİYA İŞEMİK İNSULT ZAMANI VENADAXİLİ TROMBOLİZİSDƏN SONRA MƏNFİ NƏTİCƏNİN MÜSTƏQİL PREDİKTORU SAYILIRMI?

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Proteinuriyası olan və yumaqcıq filtrasiyasının sürəti azalmış xəstələr yüksək insult riskinə malikdirlər. Təqdim olunmuş tədqiqatın məqsədi rutin klinik tədqiqatda venadaxili trombolizis olunmuş xəstələrdə işemik insultun mənfi nəticəsinin prediktorlarından biri kimi yumaqcıq filtrasiyanın sürətinin azalmasından başqa, proteinuriyanın rolunu öyrənmək üçün ədəbiyyatın tədqiqi olmuşdur. Proteinurya işemik insult zamanı venadaxili trombolizisdən sonra mənfi nəticənin müstəqil prediktorudur və xroniki böyrək xəstəliyinin trombolitik terapiyanın effektivliyinə əhəmiyyətli dərəcədə təsirini göstərir.

Açar sözlər. işemik insult, serebro-renal disfunksiya, proteinuriya, yumaqcıq filtrasiyası sürəti, venadaxili trombolizis, hemorragik transformasiya.

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