

## EVALUATION OF EARLY ISCHEMIC CHANGES IN STROKE PATIENTS TREATED WITH THROMBOLYTIC THERAPY

Kolevski Goran,<sup>1</sup> Korneti-Pekevaska Kostandina<sup>2</sup>

<sup>1</sup> Clinic of Neurology, Clinical center Skopje, R. Macedonia

<sup>2</sup> Institute of Anatomy, Medical Faculty University “Sts Cyril and Methodius”, Skopje, R. Macedonia

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**Abstract: Introduction:** The aim of this study is to evaluate early brain ischemic changes on CT scan in stroke patients in correlation with the clinical outcome, as well as to evaluate if there is prognostic and predictive features that can be used. **Patients and methods:** We examined 20 patients with acute ischemic stroke, from which 12 were male and 8 were female, at the age from 47 to 76 years. **Results:** The hyperdense medial artery (HMA) sign was present in 10 (50%) patients. Concerning the ASPECTS score, 5 patients (25%) had normal score of 10 points, while 7 patients (35%) had score of 7 points. 12 patients (60%) had unfavorable outcome, while 8 patients (40%) had favorable outcome. Our statistical analysis shows that age of more than 65 years, presence of 2 or more risk-factors, ASPECTS score of 7 and presence of HMA sign were all statistically significant predictors of unfavorable outcome in examined patients ( $p < 0.05$  each). The presence of the hyperdense medial artery sign was the most significant single predictor for unfavorable clinical outcome ( $p = 0.0042$ ,  $p < 0.05$ ). **Conclusion:** The presence of HMA sign is the most significant single predictor for unfavorable clinical outcome.

**Key words:** stroke; hyperdense medial artery sign; outcome; thrombolysis.

### INTRODUCTION

Acute ischemic stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery. This is a clinical emergency that requires prompt diagnosis and treatment (1).

Acute ischemic stroke is one of the most important causes of death and long-term disability in the

world. According to the World Health Organization (WHO), 15 million people suffer from stroke worldwide each year (2). Of these, 5 million die, and around 5 million are permanently disabled. Acute ischemic stroke constitutes approximately 85% of all strokes. Contemporary and comprehensive management of ischemic stroke require prompt access to neuroimaging and thrombolytic therapy.

Neuroimaging plays a very significant role in the evaluation of patients suspected of acute ischemic stroke. Computed tomography (CT) is the first line diagnostic test for the emergency evaluation of acute stroke due to accuracy of imaging, widespread availability and its low cost (3).

There are subtle changes on non-contrast CT that can be used for prompt diagnosis of acute ischemic stroke. Those changes are hypoattenuation of areas in brain parenchyma, cortical swelling with sulcal effacement, loss of gray-white matter differentiation, as well as hyperdense medial cerebral artery sign (4).

Alberta Stroke Program Early CT score (ASPECTS) is a clinical tool that uses non-contrast CT for evaluation of early ischemic brain changes. This is a 10-point medial artery zone quantitative topographic CT scan score (5, 6). ASPECTS offers the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes on pretreatment CT studies in patients with acute ischemic stroke of the anterior circulation. To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischemic change for each of the predefined brain regions. ASPECTS score of 10 means that there are no early ischemic changes. This score is widely recognized and used in many studies (7, 8, 9).

Another tool for evaluation of early brain ischemic changes is the hyperdense medial artery (HMA) sign (Figure 1) (10). It has been known to be an indica-



**Figure 1.** Hyperdense media artery (HMA) sign

tor of occluding clot in cases of acute ischemia on non-enhanced CT, for a long time. Additionally, it is the earliest sign, and is visible long before early parenchymal changes. HMA sign becomes visible within the onset of occlusion in a medial cerebral artery M1-segment. The histopathological analogue for the HMA sign is a thrombus occluding the vessel.

Evidence from a numerous studies suggest that early ischemic changes on non-contrast CT before the administration of intravenous thrombolysis can predict functional outcome of patients (11).

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has been widely accepted and used as a safe and effective treatment in patients whose onset of symptoms is within 4.5 h. Nowadays, diagnostic imaging technologies play an important role in determining which patient will have the greater benefit from administering the thrombolytic medication (12, 13).

**The aim of our study** was to evaluate these changes in correlation to clinical outcome of patients, as well as to evaluate if there is a prognostic and predictive features that can be used.

## PATIENTS AND METHODS

In this study, we examined 20 patients with acute ischemic stroke, treated at the Clinic of neurology-Skopje, Macedonia, in the period from June to November 2015. Non-contrast CT was used to detect early ischemic changes and to exclude intracerebral hemorrhage. All patients fulfilled criteria for thrombolytic treatment and received appropriate intravenous thrombolytic therapy recombinant tissue plasminogen activator (Actilyse / rt-PA, Boehringer Ingelheim, Germany). This therapy was given using standard protocol (0.9 ml/kg; 10% in bolus, 90% in 1 hour infusion). The outcome was measured using the modified Rankin Scale (mRS) which is commonly used for measuring

the degree of disability or dependence in patient with stroke (14). A 3-month follow-up status was measured by the mRS and then dichotomized into either favorable (mRS  $\leq 2$ ) or unfavorable (mRS  $> 2$ ) outcome groups.

Non-contrast CT findings indicating early ischemic changes for each patients were analyzed with ASPECTS grading system as well as HMA sign.

Age and presence of risk factors (hypertension, hyperlipidemia, previous stroke or TIA, previous myocardial infarction, diabetes, smoking) as variables that can influence the outcome were also evaluated.

Standard statistical methods for descriptive statistics were used, as well as determination of correlation between examined data groups. Also, logistic regression analysis was used in order to evaluate the probability to determine the outcome. P values of  $< 0.05$  were considered as statistically significant.

## RESULTS

We examined 20 patients with acute ischemic stroke, from which 12 were male and 8 were female, at the age from 47 to 76 years (mean age  $61 \pm 11$  SD). 12 patients (60%) were older than 65 years. Presence of these risk-factors were evaluated: hypertension, hyperlipidemia, previous stroke or TIA, previous myocardial infarction, diabetes and smoking. The most present risk-factor was hypertension (12/60%), followed by hyperlipidemia and smoking (8/40% each). Also, from the total of 20 patients, 12 patients (60%) had 2 or more risk-factors.

The hyperdense medial artery (HMA) sign was present in 10 (50%) patients.

Concerning the ASPECTS score, 5 patients (25%) had normal score of 10 points, while 7 patients (35%) had score of 7 points. There were no patients with ASPECTS score lower than 7. According to guidelines for thrombolytic therapy, it is contraindicated to give this therapy when there are early ischemic changes over one-third of brain hemisphere (ASPECTS score  $< 7$ ).

The outcome was measured using the mRS, at 3<sup>rd</sup> month after the ischemic stroke, and results where dichotomized into either favorable (mRS  $\leq 2$ ) or unfavorable (mRS  $> 2$ ) outcome groups. 12 patients (60%) had unfavorable (mRS  $> 2$ ) outcome, while 8 patients (40%) had favorable (mRS  $\leq 2$ ) outcome.

There was statistically significant correlation between age (especially age of more than 65 years) and presence of risk-factors (especially presence of 2 or more risk-factors), in relation to the outcome ( $p < 0.05$  both). Also, there was statistically significant correlation between ASPECTS score values and the outcome ( $p < 0.05$ ). We use Fisher's exact test when we analyzed the presence of HMA sign in relation to outcome.

Results confirmed that there is a statistically significant relationship between presence of hyperdense medial artery (HMA) sign and unfavorable outcome.

We also describe the relationship between the outcome, presented as dependent dichotomous variable of mRS [favorable (mRS  $\leq$  2) or unfavorable (mRS  $>$  2) outcome] on one side, and measured independent variables (age, presence of risk factors, ASPECTS and HMA sign) on other side. For this purpose we used the logistic regression analysis. This statistical analysis shows that age of more than 65 years, presence of 2 or more risk-factors, ASPECTS score of 7 and presence of HMA sign were all statistically significant predictors of unfavorable outcome in examined patients ( $p < 0.05$  each). Also, ASPECTS score of more than 7 points was found not to be significant prediction factor for favorable outcome ( $p = 0.42$ ). The presence of the hyperdense medial artery (HMA) sign was the most significant single predictor for unfavorable clinical outcome ( $p = 0.0042$ ,  $p < 0,05$ ) (Table 1).

**Table 1.** Clinical variables of patients with favourable or unfavourable functional outcomes

Clinical variables	mRS $\leq$ 2 favourable outcome (n.of patients)	mRS $>$ 2 unfavourable outcome (n. of patients)
Age $>$ 65 y.	2	10
Age $\leq$ 65 y.	6	2
Risk-factors $\geq$ 2	2	10
Risk-factors $<$ 2	6	2
ASPECTS 7	1	6
ASPECTS $>$ 7	7	6
HMA sign present	1	9
HMA sign absent	7	3

ASPECTS - Alberta Stroke Program Early CT Score; HMA sign - Hyperdense Medial Artery sign; mRS - modified Rankin Scale

## DISCUSSION

Early brain ischemic changes can be evaluated using the non-contrast CT. This is of great importance, because it allows to get early diagnostic data of patients in acute phase of stroke. After that, appropriate therapeutic measures can be used. ASPECTS score and HMA signs are widely used CT parameters in neuroimaging. Their clinical significance is confirmed in many studies.

Prediction of outcome as guideline for further treatment is needed for all patients who are suspected of

acute ischemic stroke, because treatment decision is made in the acute stage when the final diagnosis is still unclear (15, 16).

Our results confirmed that there is a good correlation between age, presence of risk-factors, and also ASPECTS score points and presence of HMA sign (17).

We have selected prediction factors that are widely available to the neurologists in the acute stage, that are very helpful in managing patients with stroke (18). Concerning the possibility of predicting the outcome, our results showed that presence of HMA sign can be used for this purpose. In our study, we confirmed that presence of the hyperdense medial artery (HMA) sign is the most significant single predictor for unfavorable clinical outcome. Also, age of more than 65 years, presence of 2 or more risk-factors and ASPECTS score of 7 can be used as predictors of unfavorable outcome in patients with acute stroke. In his work, Milosavljevic and Ivkovic examined the role of CT brain perfusion in cases of acute brain stroke following thrombolytic therapy, in which they successfully saved ischemic penumbra in their patients. This will be our goal for future work in the field of acute stroke therapy. Our results are in concordance with several other studies (19, 20, 21, 22).

## CONCLUSION

We can conclude that age of more than 65 years, presence of 2 or more risk-factors, ASPECTS score of 7 and presence of HMA sign are all statistically significant predictors of unfavorable outcome in examined patients. The presence of HMA sign is the most significant single predictor for unfavorable clinical outcome. Those prediction factors can be used for further planning appropriate measures, in order to achieve the best possible therapeutic solutions for patients with acute ischemic stroke.

## Conflict of interest

The authors declare that there are no conflicts of interest.

## Abbreviations

**WHO** — World Health Organization

**CT** — Computed tomography

**ASPECTS** — Alberta Stroke Program Early CT score

**HMA** — hyperdense cerebral media artery

**mRS** — modified Rankin Scale

## Sažetak

## EVALUACIJA RANIH ISHEMIJSKIH PROMENA KOD PACIJENATA SA MOŽDANIM UDAROM TRETIRANIH TROMBOLITIČKOM TERAPIJOM

Kolevski Goran,<sup>1</sup> Korneti-Pekevka Kostandina<sup>2</sup>

<sup>1</sup> Clinic of Neurology, Clinical center Skopje, R. Macedonia

<sup>2</sup> Institute of Anatomy, Medical Faculty University "Sts Cyril and Methodius", Skopje, R. Macedonia

**Uvod:** Cilj ove studije je evaluacija ranih ishemičnih promena mozga upotrebom kompjuterizovane tomografije, kod pacijenata sa akutnim moždanim udarom, u korelaciji sa kliničkim ishodom, kao i procena pojedinih prognostičkih parametara. **Pacijenti i metode:** Ispitali smo 20 pacijenata sa akutnim ishemijskim moždanim udarom, od kojih 12 muškog, a 8 ženskog pola, starosti od 47 do 76 godina. **Rezultati:** Hiperdenzni znak medijalne cerebralne arterije je bio prisutan kod 10 (50%) pacijenata. U odnosu na ASPECTS skor, 5 pacijenata (25%) su imali normalan skor od 10 poena, dok je 7 pacijenata (35%) imalo skor od 7 poena. 12 pacijenata (60%) je imalo nepovoljan ishod, dok je 8 pacijenata (40%) imalo povoljan ishod.

Statistička analiza podataka pokazala je da uzrast od preko 65 godina, prisutvo 2 ili više faktora rizika, ASPECTS skor od 7 i prisustvo hiperdenznog znaka medijalne cerebralne arterije su bili statistički signifikantni prediktori za nepovoljan ishod ( $p < 0,05$  svaki). Prisustvo hiperdenznog znaka medijalne cerebralne arterije je bio najznačajniji pojedinačni prediktor nepovoljnog ishoda kod ispitivanih pacijenata ( $p = 0,0042$ ;  $p < 0,05$ ). **Zaključak:** Prisustvo hiperdenznog znaka medijalne cerebralne arterije jeste najznačajniji prediktor za nepovoljni klinički ishod.

**Cljučne reči:** moždani udar, hiperdenzni znak medijalne cerebralne arterije, ishod, trombolitička terapija.

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**Correspondence to / Autor za korespondenciju**

Kolevski Goran, MD, MSc;  
Clinic of Neurology, Clinical center Skopje, Macedonia  
bul. Vodnjanska 18, 1000 Skopje, Macedonia  
e-mail: gogomk@hotmail.com;  
phone: ++389 75 481025;