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Free-Radical Processes in Stroke Patients with Vascular Comorbidity

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Abstract

Acute oxygen and glucose deficiency during brain ischemia leads to the inability of neurons producing a sufficient amount of adenosine triphosphate (ATP) using an oxidative metabolism. Energy deficiency leads to neuronal death via different mechanisms including oxidative stress. This study aimed to evaluate the changes and main characteristics of free-radical processes in patients with acute stroke and transient ischemic attacks (TIA) in the presence of vascular comorbidity. One hundred forty-one patients with stroke (male—72, mean age—65.48±13.44 years) and with a history of cardiovascular diseases (CVD). Free-radical formation was assessed in plasma based on oxidative (chemiluminescence intensity index—basal [CIIb] and zymosan-stimulated [CIIs]) and lipid-peroxidation markers (antiperoxide plasma activity [APA] and malondialdehyde [MDA]). During the follow-up period (from 6 to 72 months) the incidence of recurrent cardiovascular events, outcomes, and survival were assessed using a telephone interview. All patients who survived were rehospitalized and underwent neurologic assessment. A high level of vascular comorbidity was demonstrated. The level of imbalance of free-radical processes correlated with an acute-stroke severity with a maximal intensity of lipid peroxidation in hemorrhagic stroke and the activation of oxidative stage of free-radical processes in ischemic stroke. There was a significant decrease of APA in both types of stroke, whereas TIA was characterized by maintenance of high APA levels ($p < 0.05$). In patients with an acute-stroke free-radical imbalance increased proportional to the level of a vascular comorbidity. The decrease of APA level and increase of MDA level, which reflect significant oxidative imbalance and more extensive vascular damage, correlate with inferior recovery during the inpatient period ($r = 0.357$; $p < 0.05$ и $r = 0.234$; $p < 0.001$ respectively). It was demonstrated that low MDA and high APA level in patients with acute stroke are the prognostic markers of a good functional recovery during inpatient treatment and decreased stroke-associated mortality during long-term follow-up.

Keywords: Stroke; Vascular comorbidity; Free-radical processes

Introduction

Stroke is a disabling cerebrovascular disease with a mortality rate reaching up to 54% and disability rate of 50-80% [1,2]. The decrease of stroke morbidity and increase of treatment efficacy is a priority task of practical health care [3].

Cerebral hypoxia and ischemia with the decrease of aerobic glycolysis resulting from the termination of a cerebral perfusion are the key pathologic processes in stroke [4]. Resulting energy-synthesis deterioration leads to imbalance of free-radical processes with the development of oxidative stress [5,6].

Vascular pathology, associated with atherosclerosis, arterial hypertension, and diabetes mellitus (DM) usually develops in multiple vessels of the organism simultaneously [7,8]. The presence of several cardiovascular conditions in one patient is referred as comorbidity (in Latin, *Co* means together, *morbus* means disease), which can adversely affect the course of acute stroke, associated outcomes, and prognosis [9].

Energy-synthesis imbalance in cells and tissues promotes a significant change in free-radical processes, which are widely recognized as a key component of the development and maintenance of postischemic cerebral disorders and also of hypertension, DM, atrial fibrillation (AF) and coronary artery disease (CAD) [10-12].

At present, data on the changes and characteristics of free-radical processes in patients with acute stroke and transient ischemic attacks (TIA) with different severity of vascular comorbidity are lacking.

The aim of this study was to evaluate the changes and main characteristics of free-radical processes in patients with acute stroke and transient ischemic attacks (TIA) in the presence of vascular comorbidity.

Methods

One hundred forty-one patients with acute stroke and TIA of different severity aged 28-94 years (mean age—65.48±13.44 years) including 72 (51.1%) men and 69 (48.9%) women were admitted to the intensive-care department in 2009-2012. Ischemic stroke (IS) was diagnosed in 87 (61.7%); hemorrhagic stroke (HS), in 35 (24.8%); and TIA, in 19 (13.5%) patients.

Stroke type was determined using computer/magnetic-resonance tomography (CT/MRT), clinical evaluation, and patient-history data.

Daily clinical monitoring was performed in all patients, including history and complaints assessment, blood pressure, pulse, respiratory rate, electrocardiogram and body temperature control, complete blood count, and blood chemistry. Neurologic evaluation was performed using NIH-NINDS scales; functional status and recovery were assessed according to modified Renkin scale. Free-radical processes were assessed in serum at several time points on oxidative markers (indices of active oxygen-species formation in leukocytes—basal (ILCLIb) and zymosan-stimulated (ILCLIs) indices of leukocyte chemiluminescence intensity, and lipid peroxidation markers (index of antiperoxidation plasma activity [APA] and malondialdehyde [MDA]). The control group consisted of 33 healthy volunteers.

During the follow-up period (ranging from 6 months to 6 years) a telephone interview with 45 (31.9%) of 141 originally evaluated patients was performed. Survival, the incidence of recurrent cardiovascular accidents, and outcomes were assessed.

Results and Discussion

Vascular comorbidity level was assessed in all patients with acute stroke and TIA. Analysis revealed a high basal comorbidity level in the majority of patients (Table 1).

There was a significant free-radical imbalance in stroke and TIA patients on admission, including both oxidation and lipid-peroxidation markers. There were several differences between stroke types. It is important to note that TIA patients demonstrated significant differences only on oxidation markers compared to the normal group, with ILCLIb 1.73-fold lower than in the control group ($p < 0.05$), 1.29-fold lower than in IS group ($p < 0.01$), and 2.17-fold lower than in HS group ($p < 0.01$). ILCLIs level in TIA patients was 1.52-fold higher compared to normal levels ($p < 0.05$).

MDA and APA levels were intact in TIA patients on day 1 after admission. MDA level in IS patients was 1.37-fold higher ($p < 0.001$); in HS patients—1.48-fold higher compared to TIA group ($p < 0.001$) with no significant differences on MDA levels between IS and HS groups. APA level was 1.1-fold lower in IS group ($p < 0.05$) and 1.19-fold lower in HS group compared to the control group ($p < 0.05$) (Figure 1).

This suggests a preserved functioning of endogenous protective antioxidant system in patients with TIA, which prevents postischemic brain-tissue damage with temporary functional deterioration in TIA as a result of transient energy–production imbalance. The activation of endogenous antioxidant-protection system neutralizes metabolic disturbances, preventing the progression of postischemic apoptosis.

ILCLIb in patients with vascular comorbidity demonstrates a progressive decrease proportional to the increase in the number of cardiovascular conditions. In patients with three cardiovascular diseases (CVDs) ILCLIb was 1.20-fold lower; and in patients with four CVDs—1.75-fold lower ($p < 0.05$) compared to stroke patients with comorbid hypertension only. In patients with two to four CVDs, ILCLIs was the highest. MDA level increased proportionally to the number of comorbid CVDs; protective APA demonstrated the most prominent decrease in patients with four or more CVDs, reflecting a robust depletion of protective-antioxidant reserves and oxidative stress–correction capacities. Thus, in acute-stroke patients, free-radical imbalance increases proportionally to the level of cardiovascular comorbidity, demonstrating maximal levels in patients with four CVDs, which reflects a 1.66-fold decrease of ILCLIb, 1.41-fold decrease of APA , a 1.35-fold increase of ILCLIbs, and 1.57-fold increase of MDA ($p < 0.05$) (Figure 2).

A significant correlation of the number of diagnosed CVDs with ILCLIb levels ($r = –0.249$; $p < 0.01$), MDA ($r = 0.240$; $p < 0.01$), and APA ($r = –0.201$; $p < 0.05$) was observed. The decrease of APA and increase of MDA levels, characteristic to the progressive free-radical imbalance with the increase of the number of organs involved into pathologic cardiovascular process demonstrate a positive correlation with inferior recovery during inpatient treatment ($r = 0.357$; $p < 0.05$ and $r = 0.234$; $p < 0.001$, respectively).

Therefore an increase of free-radical imbalance was observed in patients with acute stroke and TIA, proportional to the level of vascular comorbidity.

The assessment of free-radical processes' characteristics in patients with comorbidity revealed that a decrease of APA on admission was associated with inferior functional outcome on Renkin scale. In patients with low APA, good functional outcome (Renkin 0) was observed in 26.2% cases; unfavorable functional outcome (Renkin 5), in 64.7% cases ($r = 0.234$; $p < 0.05$). The MDA level also demonstrated a correlation with observed outcome: MDA was significantly increased only in 16.0% of patients with good functional outcome compared to 52.9% of patients with unfavorable outcome ($r = 0.357$; $p < 0.001$) (Figure 3).

Pre-existing diseases	Ischemic stroke, $n = 87$	Hemorrhagic stroke, $n = 35$	TIA, $n = 19$	P	Total, $n = 141$
Hypertension	86 (98.9%)	32 (91.4%)	17 (89.5%)	0.064	135 (95.7%)
CAD, cardiosclerosis, angina *	63 (72.4%)	17 (48.6%)	6 (31.6%)	0.001	86 (60.9%)
AF *	31 (35.6%)	2 (5.7%)	0	0.001	33 (23.4%)
DM	23 (26.4%)	6 (17.1%)	4 (21.1%)	0.530	33 (23.4%)
Acute stroke (history of IS/HS) *	25 (28.7%)	1 (2.9%)	0	0.001	26 (18.4%)
Postinfarction cardiosclerosis (PC)	20 (23.0%)	3 (8.6%)	2 (10.5%)	0.114	25 (17.7%)
Comorbidity					
Hypertension + CAD, angina*	63 (72.4%)	16 (45.7%)	6 (31.6%)	0.001	85 (60.3%)
Hypertension + AF*	31 (35.6%)	2 (5.7%)	0	0.001	33 (23.4%)
Hypertension + CAD, angina + AF*	30 (34.5%)	2 (5.7%)	0	0.001	32 (22.7%)
Hypertension + DM	23 (26.4%)	5 (14.3%)	4 (21.1%)	0.344	32 (22.7%)
Hypertension + PC	20 (23.0%)	2 (5.7%)	2 (10.5%)	0.052	24 (17.0%)
Hypertension + PC + AF	8 (9.1%)	1 (2.9%)	0	0.204	9 (6.4%)
Hypertension + PC + DM	8 (9.1%)	1 (2.9%)	2 (10.5%)	0.445	11 (7.8%)
Hypertension + CAD + AF +DM	8 (9.1%)	1 (2.9%)	0	0.204	9 (6.4%)
Hypertension +CAD+AF+DM +PC	3 (3.4%)	1 (2.9%)	0	0.714	4 (2.8%)
PC + DM	8 (9.1%)	1 (2.9%)	0	0.204	9 (6.4%)
Total*	79 (90.8%)	20 (57.1%)	6 (31.6%)	0.001	105 (74.5%)
Control group (no comorbidity)					
Hypertension only*	8 (9.2%)	15 (42.9%)	13 (68.4%)	0.001	36 (25.50%)

Note: absolute numbers are presented (n—%)
*—$p < 0.05$.

Table 1: Comorbidity level in patients with acute stroke and TIA

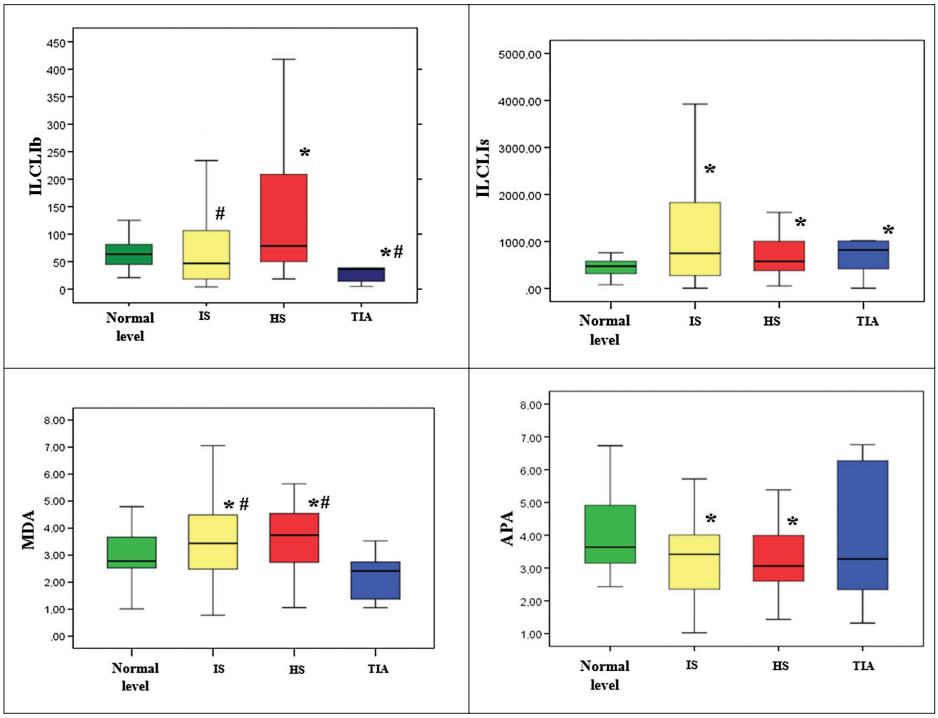

Figure 1: Free-radical markers in acute stroke patients depending on stroke type (*—$p < 0.05$—compared to control group; #—$p < 0.05$—between groups)

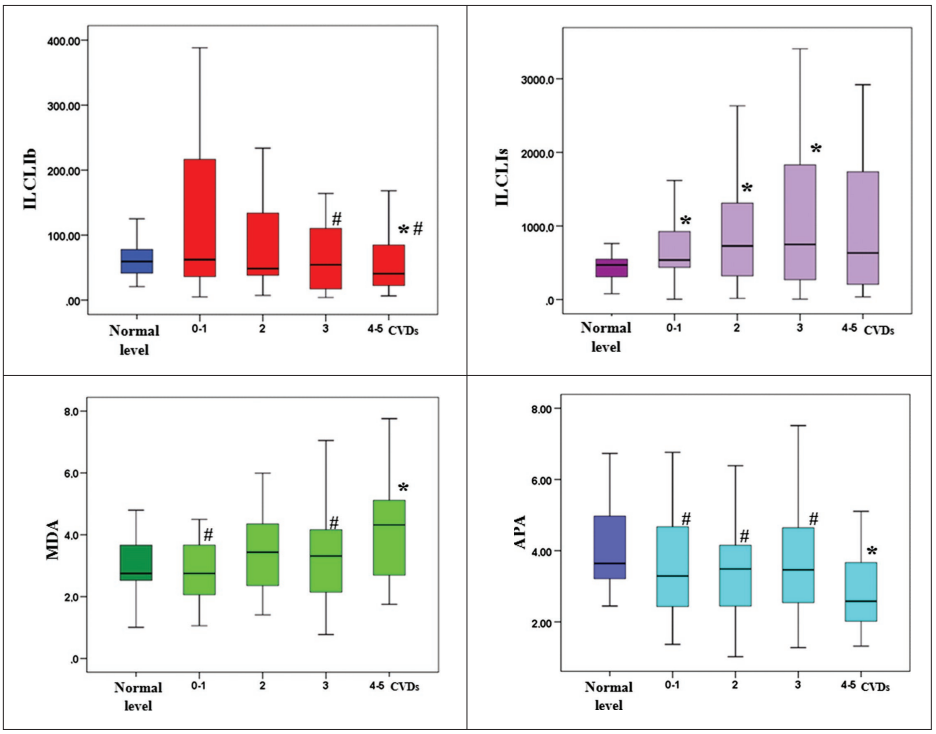

Figure 2: Free-radical process markers in patients with acute stroke and TIA, depending on the number of comorbid CVDs (*—$p < 0.05$—compared to normal level; #—$p < 0.05$—compared to the group of patients with four or more CVDs)

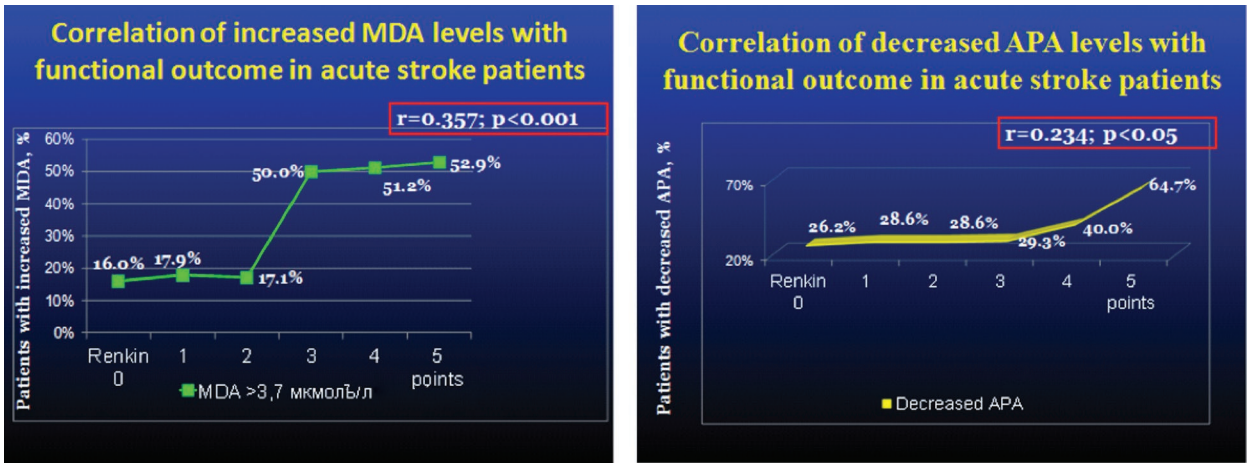

Figure 3: Correlation of decreased APA levels and increased MDA levels with functional outcome in acute-stroke patients

Outcome	Number of CVDs				Total
	One	Two	Three	Four or more	
Survived	11 (91.7%)	6 (54.5%)	9 (60.0%)	4 (57.1%)	30 (66.7%)
Died	1 (8.3%)	5 (45.5%)	6 (40.0%)	3 (42.9%)	15 (33.3%)
Total	12 (26.7%)	11 (24.4%)	15 (33.3%)	7 (15.6%)	45 (100%)

Table 2: Outcomes of patients with acute stroke and TIA during a 6-year follow-up period depending on the number of CVDs

Follow-up evaluation

During the 6 years of follow-up period after the initial stroke, 32.6% of patients died. The majority of patients died during the first year after discharge (nine of 15; 60%), which is 2.25-fold and 4.51-fold higher compared to the 2-3 and 4-6-year periods, respectively ($p < 0.05$).

Survival rate in patients with one CVD was 2.8-fold higher; in patients with two and less than two CVDs—1.42-fold higher, compared

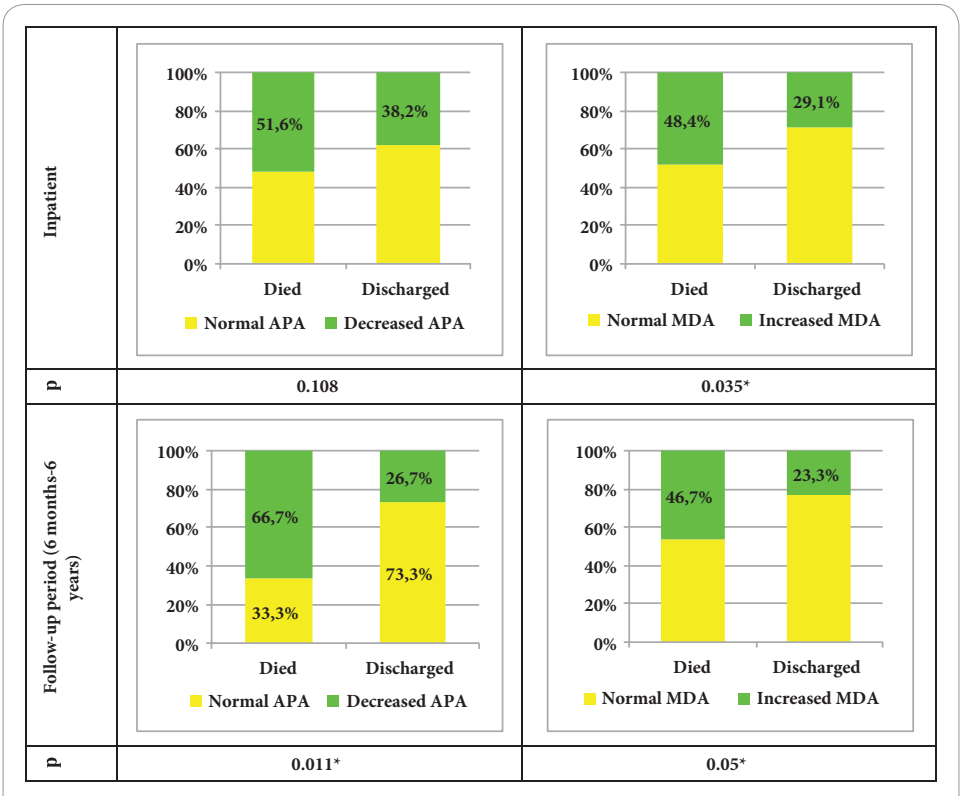

Figure 4: Prognostic role of APA and MDA

to patients with four or more CVDs ($p < 0.05$). Mortality increased in patients with more diagnosed CVDs (Table 2).

Markers of lipid peroxidation demonstrated the highest negative prognostic value both during the inpatient and follow-up periods (6 months to 6 years). An increase of lipid membrane–peroxidation marker (MDA) was associated with an unfavorable outcome during the inpatient period, whereas the depression of protective APA level on admission was associated with a negative prognosis in the long-term period (Figure 4).

Conclusion

It was demonstrated that low MDA (<3.5 mMOL/L) and high APA (>3 r.u.) levels in patients with acute stroke are prognostic markers of good functional recovery during inpatient treatment and decreased stroke-associated mortality during long-term follow-up. Marked free-radical imbalance in acute-stroke patients correlates with the level of vascular comorbidity and reflects the severity of oxidative stress and glycolysis disturbance, which may be considered a pathologic justification of long-term high-dose antioxidant therapy with energy-correction properties.

Severe cardiovascular comorbidity (combination of hypertension, CAD, PC, AF and DM), diagnosed in a majority of patients at the moment of stroke, substantiates the need for active multidisciplinary prevention strategies in the outpatient stage. Besides, severe cardiovascular comorbidity in acute stroke patients should be regarded as a significant prognostic factor for negative rehabilitation outcome.

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