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ARTICLE

Clinical and molecular correlates of the ASPECTS in the acute phase of stroke

Correlação clínica e molecular com a ASPECTS na fase aguda do acidente vascular cerebral

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ABSTRACT

Background: The Alberta Stroke Program Early CT Score (ASPECTS) scale was developed for monitoring early ischemic changes on CT, being associated with clinical outcomes. The ASPECTS can also associate with peripheral biomarkers that reflect the pathophysiological response of the brain to the ischemic stroke. **Objective:** To investigate the association between peripheral biomarkers with the Alberta Stroke Program Early CT Score (ASPECTS) in individuals after ischemic stroke. **Methods:** Patients over 18 years old with acute ischemic stroke were enrolled in this study. No patient was eligible for thrombolysis. The patients were submitted to non-contrast CT in the first 24 hours of admission, being the Alberta Stroke Program Early CT Score and clinical and molecular evaluations applied on the same day. The National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale and the Mini-Mental State Examination for clinical evaluation were also applied to all subjects. Plasma levels of BDNF, VCAM-1, VEGF, IL-1β, sTNFRs and adiponectin were determined by ELISA. **Results:** Worse neurological impairment (NIHSS), cognitive (MEEM) and functional (Rankin) performance was observed in the group with changes in the NCTT. Patients with NCTT changes also exhibited higher levels of IL-1β and adiponectin. In the linear multivariate regression, an adjusted R coefficient of 0.515 was found, indicating adiponectin and NIHSS as independent predictors of ASPECTS. **Conclusion:** Plasma levels of adiponectin are associated with the ASPECTS scores.

Keywords: Brain Ischemia; Neurology; Biomarkers; Neurologic Examination; Prognosis.

RESUMO

Introdução: A Alberta Stroke Early Score (ASPECTS) foi desenvolvida para monitorização de alterações isquêmicas precoces na tomografia computadorizada de crânio, estando associada a desfechos clínicos. A ASPECTS também pode se associar aos biomarcadores periféricos que refletem a resposta fisiopatológica do cérebro ao AVC isquêmico. **Objetivo:** Investigar à associação entre os parâmetros periféricos com a Alberta Stroke Early Score (ASPECTS) em indivíduos após acidente vascular cerebral isquêmico. **Métodos:** Pacientes acima de 18 anos com AVC isquêmico agudo foram incluídos neste estudo. Nenhum paciente foi elegível para trombólise. Os pacientes foram submetidos à tomografia computadorizada sem contraste nas primeiras 24 horas da admissão, a ASPECTS e as avaliações clínicas e moleculares aplicadas no mesmo dia. O National Institutes of Health Stroke Scale (NIHSS), a escala de Rankin modificada e o Mini Exame do Estado Mental para avaliação clínica também foram aplicados a todos os indivíduos. Os níveis plasmáticos de BDNF, VCAM-1, VEGF, IL-1β, sTNFRs e adiponectina foram determinados por ELISA. **Resultados:** Pior desempenho neurológico (NIHSS), cognitivo (MEEM) e funcional (Rankin) foram observados no grupo com alterações na ASPECTS. Pacientes com alterações na ASPECTS também exibiram níveis mais altos de IL-1β e adiponectina. Na regressão multivariada linear, foi encontrado um coeficiente R ajustado de 0,515, indicando adiponectina e NIHSS como preditores independentes para a ASPECTS. **Conclusão:** Os níveis plasmáticos de adiponectina estão associados aos escores da ASPECTS.

Palavras-chave: Isquemia Encefálica; Neurologia; Biomarcadores; Exame Neurológico; Prognóstico.

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The non-contrast computed tomography of the skull (NCCT) is the diagnostic procedure of choice for the evaluation of stroke in emergency situations. It is fast and widely available, not requiring contrast[1,2,3]. Moreover, NCCT is highly sensitive for intracerebral hemorrhage detection, being the most used neuroimaging method for the selection of patients with ischemic stroke for thrombolysis[4,5,6].

The Alberta Stroke Program Early CT Score (ASPECTS) scale was developed for detection and quantification of early ischemic changes on NCCT[6,7]. This instrument contributes to stratify the risk for hemorrhagic transformation of brain ischemic areas and assist in the interpretation of the criteria for thrombolysis[6,7,8]. The ASPECTS is especially useful to quantify ischemic signs in the territory of the middle cerebral artery, the most often affected area in stroke[7,8]. Importantly, the ASPECTS has been consistently associated to clinical outcomes[6].

The acute ischemic region is highly dynamic. Neuronal cells can lose their function in a few minutes, leading to neurological signs and impairment[9,10,11,12,13,14,15,16,17]. Post-stroke inflammation may contribute to both ischemic injury extension and brain recovery[4,9,16,17,18,19,20,21]. Blood-based biomarkers, including inflammation-related markers, have been associated to the volume of cerebral infarction and severity of neurological deficits[3,4,10,12,17]. A growing literature on stroke biomarkers has emerged, but no blood-based predictive biomarker was validated in the acute phase of stroke[17,22].

Considering the predictive value of the NCCT[6], this exploratory study aimed at evaluating whether blood-based or peripheral biomarkers are associated to the ASPECTS. Our hypothesis is that ASPECTS is associated to peripheral biomarkers that reflect the pathophysiological response of the brain to the ischemic stroke.

METHODS

Patients

Patients over 18 years old with the diagnosis of ischemic stroke (ictus time <24 hours) admitted at the Stroke Unit, Risoleta Tolentino Neves Hospital (Belo Horizonte City, Minas Gerais State) from January to June 2015, were eligible for the study. No patient was eligible for thrombolysis due to the prolonged ictus time (>4 hours) at hospital arrival.

Exclusion criteria were individuals diagnosed with ischemic stroke with hemorrhagic transformation; transient ischemic attack; diagnosis of other neurological and/or major psychiatric disorders; clinical instability. Patients with significant reduction of consciousness level according to the Glasgow Coma Scale (value less than 15); aphasia according to the National Institutes of Health Stroke Scale; delirium according to the Confusion Assessment Method were also excluded.

The study was conducted in accordance with Resolution 466/2012. The project was evaluated and approved by the Research Ethics Committee of the Federal University of Minas Gerais, Project: CAAE – 32809514.4.4.0000.5149

Assessment tools

Clinical parameters

Clinical and socio-demographic data were extracted from the medical records and/or obtained after interview with patients. Age, risk factors and pathophysiological mechanisms with the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[23] and Oxfordshire Community Stroke Project (OCSP)[24] were recorded.

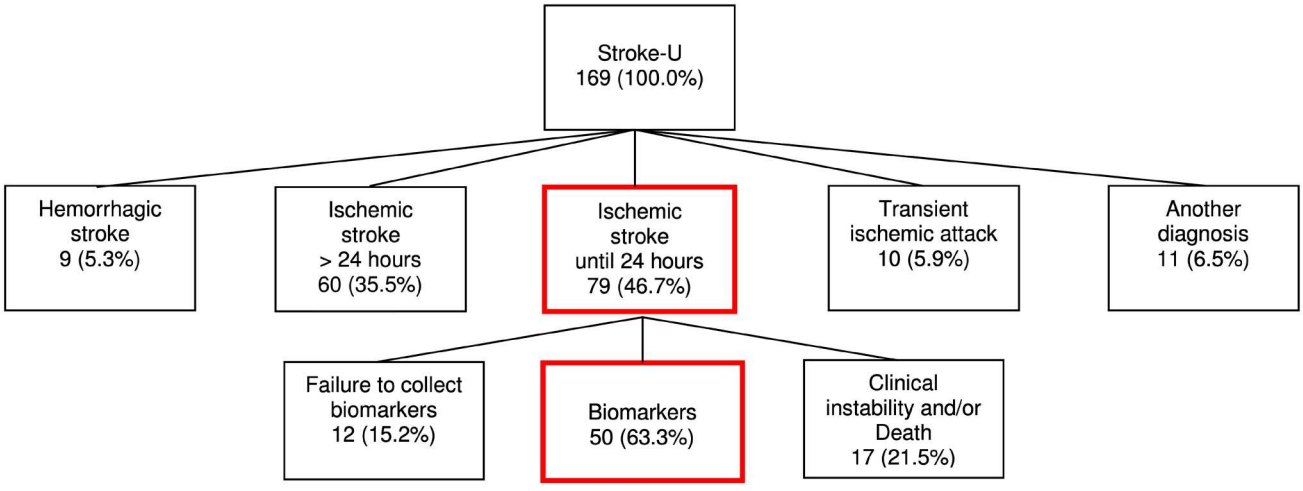

Figure 1. Number of patients included in the present study from January to July 2015.

The clinical assessment took place within the first 24 hours of ictus. The National Institutes of Health Stroke Scale (NIHSS)[25] was used to quantify the neurological impairment. The modified Rankin scale was used to quantify the degree of disability and dependence in daily life activities (DLA)[25] and the Mini-Mental State Examination (MMSE) to assess cognitive functioning[26].

The NIHSS and Rankin were applied through clinical examination/interview by two trained clinicians with good inter-observer agreement (kappa=0.850). The other clinical tools were applied by a single researcher.

Neuroimaging

All patients were submitted to the NCCT in the first 24 hours of admission. The ASPECTS[6] was applied to quantify the extension of brain tissue changes in the anterior circulation. According to the ASPECTS, the territory of the middle cerebral artery is subdivided into 10 standard regions evaluated in two cuts of the NCCT: at the height of the thalamus and basal ganglia, and just above the basal ganglia. A normal NCCT has ASPECTS score equal to 10. A zero value indicates diffuse ischemia in the whole territory of the middle cerebral artery. Patients with value lesser than or equal to 7 have a higher risk of hemorrhagic transformation and worse prognosis[6,7,8]. The ASPECTS was applied by an experienced stroke neurologist.

Measurement of inflammatory parameters

Ten milliliters of blood were drawn with venipuncture in vacuum tubes containing EDTA (Vacuplast, Huangyan, China) within the first 24 hours of admission. The blood was processed within 2 hours of sampling. These samples were then centrifuged at 3000 g for 10 min, 4°C, twice. The plasma was collected and stored at -70°C until assayed.

Plasma levels of IL-1β, sTNFR-1, sTNFR-2, VCAM-1, VEGF, Adiponectin and BDNF were measured by Enzyme-Linked Immunosorbent Assay (ELISA) according to the procedures supplied by the manufacturer (DuoSet, R&D Systems, Minneapolis, MN, USA). Concentrations were obtained against a standard curve calibrated with known amounts of protein and expressed as pg/mL, except for VCAM-1 levels, which were expressed as ng/mL. All samples were assayed in duplicate and in a single assay to avoid inter-assay variation. The intra-assay variation was under 3%. The detection limits were 3 ng/mL for VCAM-1, 5 pg/mL for adiponectin and BDNF, 3 pg/mL for IL-1β, 9 pg/mL for VEGF and 10 pg/mL for STNFR1 and STNFR2.

Statistical analysis

The categorical variables were described according to frequencies and percentages. For the statistical analysis, the SPSS v.20.0 program was used. A bilateral p-value lesser than 0.05 was adopted as statistical significance level for all tests. The variables were evaluated for normality with the Shapiro-Wilk test. Given that most variables did not show a normal distribution, non-parametric tests were used. For comparisons between different

Table 1. Socio-demographic and Clinical Characteristics of Patients with Ischemic Stroke in the Acute Phase.

Variables	Patients (n=50)	
	n	Proportion (%)
Gender		
Male	28	56
Female	22	44
Age (years)		
Mean±DPM	65.5±11.7	
Median (range)	64.5 (37–93)	
Comorbidities		
Hypertension	36	72
Tobacco Smoking**	16	32
Diabetes Mellitus	14	28
Sedentary lifestyle	11	22
Alcoholism*	8	16
Ex-Smoker**	4	8
Obesity	4	8
Arrhythmia	4	8
Atrial fibrillation	2	8
Chagas disease	2	4
Ex-Alcoholic*	2	4
Previous history of stroke	25	50
Signs of old ischemia in the brain computed tomography (TCC)	17	34
OCPS		
Partial anterior circulation	31	62
Lacunar	16	32
Posterior circulation	3	6
Total anterior circulation	0	0
TOAST		
Occlusion of small arteries	25	50
Undefined mechanism	10	20
Atherosclerosis of large arteries	8	16
Cardioembolic	6	12
Other etiologies	1	2
Hospital stay (days)		
Mean±DPM	10.3±6.8	
Median (range)	9.0 (4–30)	

n: number of patients; DPM: Average Standard Deviation; TCC: Brain Computed Tomography; OCSP: Oxfordshire Community Stroke Project; ECG: Glasgow Coma Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Criterion for alcoholism: consume any type and/or amount of alcohol. Ex-alcoholic: has stopped to consume any type and/or amount of alcohol for more than 1 year. **Criterion for tobacco smoking: consume any type and/or amount of tobacco. Ex-smoker: stopped to consume any type and/or amount of tobacco for more than 1 year.

groups, the Mann-Whitney test was applied. For correlations between the ASPECTS and independent variables, the Spearman test was used. Finally, the linear regression model was adjusted with the *Backward* method considering a p-value lesser than 0.20 to enter the covariates in the model. The adjustment of the model was assessed by means of adjusted R^2 statistics.

RESULTS

Fifty patients participated in the present study (Figure 1). Demographic and clinical data are shown in Table 1. The average age of patients was 65.5, and 56.0% were male. Among the clinical comorbidities, hypertension was the most common, present in 72% of them.

Table 2. Comparison between Alberta Stroke Program Early CT Score and Socio-demographic and Clinical Variables of Patients with Ischemic Stroke in the Acute Phase.

Variables	ASPECTS<10 (n=26)		ASPECTS=10 (n=24)		p-value*
	n	Proportion (%)	n	Proportion (%)	
Gender					
Male	14	(53.8)	14	(58.3)	0.783**
Female	12	(46.2)	10	(41.7)	
Age (years)					
Mean±DPM	67.1±12		63.8±11.4		0.392***
Median (range)	66 (43–93)		63 (37–82)		
Comorbidities					
Hypertension	21	(80.8)	15	(62.5)	0.211**
Tobacco Smoking[a]	9	(34.6)	7	(29.2)	0.509**
Diabetes *Mellitus*	18	(69.2)	18	(75.0)	0.757**
Sedentary lifestyle	19	(73,1)	20	(83.3)	0.501**
Alcoholism[b]	4	(15.4)	4	(16.7)	0.213**
Obesity	23	(88.5)	23	(95.8)	0.611**
Arrhythmia	2	(7.7)	2	(8.3)	1.000**
Atrial fibrillation	1	(3.8)	1	(4.2)	1.000**
Chagas disease	1	(3.8)	1	(4.2)	1.000**
Previous history of stroke	12	(46.2)	13	(54.2)	0.778**
Signs of old ischemia in the brain computed tomography (TCC)	8	(30.8)	9	(37.5)	1.000**
OCPS					
Partial anterior circulation	14	(53.8)	17	(70.8)	1.000**
Lacunar	11	(42.3)	5	(20.8)	0.372**
Posterior circulation	1	(3.8)	2	(8.3)	0.103**
Total anterior circulation	0	(0.0)	0	(0.0)	-
TOAST					
Occlusion of small arteries	10	(38.5)	15	(62.5)	1.000**
Undefined mechanism	7	(26.5)	3	(12.5)	1.000**
Atherosclerosis of large arteries	5	(19.5)	3	(12.5)	0.456**
Cardioembolic	4	(15.4)	2	(8.3)	0.669**
Other etiologies	0	(0.0)	1	(4.2)	1.000**
Hospital stay (days)					
Mean±DPM	12±7.8		8.5±5.0		0.094***
Median (range)	10 (3–30)		8 (3–22)		

TCC: Brain Computed Tomography; OCSP: Oxfordshire Community Stroke Project; ECG: Glasgow Coma Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment; [a]Criterion for tobacco smoking: consume any type and/or amount of tobacco; [b]Criterion for alcoholism: consume any type and/or amount of alcohol. *Statistical test; **Fisher exact test; ***Mann-Whitney test.

The most common pathophysiological mechanism was the occlusion of small arteries (50%).

There was no statistically significant difference in the socio-demographic and clinical characteristics between groups of patients with and without change in the NCTT (Table 2). Worse neurological impairment (NIHSS), cognitive (MEEM) and functional (Rankin) performance was observed in the group with changes in the NCTT (Table 3). Patients with NCTT changes also exhibited higher levels of IL-1β and adiponectin (Table 3).

There was a significant negative correlation between ASPECTS and NIHSS, mRankin and the levels of IL-1β and adiponectin. Conversely, there was a positive correlation between ASPECTS and BDNF levels (Table 4).

In the linear multivariate regression, an adjusted R coefficient of 0.515 was found, indicating adiponectin and NIHSS as independent predictors of ASPECTS (Table 5).

Table 3. Comparison Between Alberta Stroke Program Early CT Score and Molecular and Clinical Variables of Patients with Ischemic Stroke During Hospital Admission.

Variables	ASPECTS<10 (n=26)	ASPECTS=10 (n=24)	Z	p-value*
Molecular				
BDNF - pg/mL				
Mean±DPM	9052.4±2289.4	10449.0±2861.9	-1.709	0.087
Median (min-max)	9081.5 (3975–14531)	10679.5 (4101–14527)		
VCAM-1 - pg/mL				
Mean±DPM	469342.3±264710	595294±643039.3	-0.738	0.461
Median (min-max)	382530 (173060–1282480)	484260 (158400–3482720)		
VEGF - pg/mL				
Mean±DPM	359.4±267.4	391.2±274.6	-0.330	0.741
Median (min-max)	286.5 (20–1115)	291.6 (63–1088)		
IL-1beta - pg/mL				
Mean±DPM	10.0±15.5	3.5±7.0	-2.185	0.029**
Median (min-max)	2.5 (0–56)	0.5 (0–27)		
Adiponectin - pg/mL				
Mean±DPM	664269.2±375062.5	430270.8±229851.2	-2.214	0.027**
Median (min-max)	577450 (146700–1662900)	453650 (78100–934000)		
sTNFR1 - pg/mL				
Mean±DPM	1798.0±901.0	2397.6±1455.0	-1.660	0.097
Median (min-max)	1488 (591–4320)	2096 (690–7361)		
sTNFRII - pg/mL				
Mean±DPM	3450±1241.0	4017.7±1818.0	-1.068	0.285
Median (min-max)	3586 (1358–5805)	3957.5 (1527–7716)		
Clinics				
MEEM				
Mean±DPM	16.8±6.0	20.5±5.8	-2.000	0.045**
Median (min-max)	16 (0–30)	21 (12–29)		
NIHSS				
Mean±DPM	10.5±6.4	5.8±4.9	-3.292	0.001**
Median (min-max)	9.0 (0–30)	5.0 (0–21)		
Rankin				
Mean±DPM	3.3±1.5	2.4±1.5	-2.515	0.012**
Median (min-max)	4.0 (0–5)	3.0 (0–)		

n: number of patients; DPM: Average Standard Deviation; ASPECTS: Alberta Stroke Program Early CT Score; BDNF: Brain Derived Neurotrophic Factor; VCAM-1: Vascular Cell Adhesion Molecule-1; VEGF: Vascular Endothelial Growth Factor; IL-1b: Interleukin-1 beta; sTNFR1: receptors of Tumor Necrosis Factors 1; sTNFRII: receptors of Tumor Necrosis Factors 2; MEEM: Mini-Mental State Examination; BAF: Frontal Assessment Battery; NIHSS: National Institutes of Health Stroke Scale; Rankin: Modified Rankin Scale; *Statistical test; **Mann-Whitney test.

DISCUSSION

The current results showed that the ASPECTS is associated to clinical and peripheral molecular markers. This study corroborates the robust literature on the association between the extension of the stroke, as assessed by the ASPECTS, and the severity of the neurological impairment, as evaluated by the NIHSS[6,7,8]. Furthermore, it supports our original hypothesis that ASPECTS is associated to peripheral biomarkers, i.e., plasma levels of adiponectin, in the acute phase of stroke.

Several studies show that both the extension of the stroke, as assessed by the ASPECTS, and the severity of neurological impairment, as assessed by NIHSS in the first 24 hours, are reliable predictors of clinical outcome in the long term, including perception of quality of life and functionality[8,24,27]. Actually, these are highly correlated constructs as shown here and by others[8,28,29,30].

In the context of the physiological response to the brain ischemia, the inflammatory response takes place with the production and release of various pro-inflammatory cytokines[9,10,11]. For instance, preclinical[18,19,30] and clinical[30,31] studies have shown increased production of IL1-β in the first 24 hours after the stroke. In line with this, patients with NCTT changes compatible with larger ischemic area exhibited higher circulating levels of IL-1β.

In the post-stroke inflammatory response, there is also the production of anti-inflammatory and neuroprotective molecules to counterbalance and control the process. For example, stroke is associated to increased expression of BDNF, one of the main neurotrophic factors in the central nervous system, by neurons, microglia and endothelial cells in animal models[13,14,15,16]. Increased levels of BDNF have been reported in patients with stroke as well, and its levels were associated to clinical outcomes[21,31]. Interestingly, BDNF correlated with ASPECTS, but it did not remain in the final multivariate model.

Adiponectin exhibits anti-atherosclerotic, anti-inflammatory, and anti-diabetic effects[20,21,32,33,34]. High levels of adiponectin have been shown to protect against coronary artery disease[21,32]. Conversely, chronic inflammation present in obesity and metabolic syndrome inhibits the synthesis of adiponectin[20,21,32]. In the current study, higher levels of adiponectin were observed in patients with larger ischemic lesions. This is the first study to identify the association between adiponectin and the extension of brain lesion after ischemic stroke. Besides suggesting a potential role for this molecule as a prognostic biomarker, this highlights the complexity of pro- and anti-inflammatory mechanisms involved in the physiological response of the ischemic brain.

The results must be interpreted with its limitations, that include relatively small sample size and the strict selection criteria that limit its generalizability. Half of the sample had small vessel occlusion as the probable mechanism of the stroke, whereas large vessel diseases accounted for less than 20% of the cases. Conversely, the panel of molecules assessed, comprising different mechanisms and pathways, might be regarded as a strength of the study.

Table 4. Correlations Between Alberta Stroke Program Early CT Score with Molecular and Clinical Assessments of Patients with Ischemic Stroke During Hospital Admission.

Variables	Rho	p-value*
Molecular		
BDNF	0.307	0.030*
VCAM-1	0.110	0.448
VEGF	0.040	0.785
IL-1b	-0.357	0.011*
Adiponectin	-0.348	0.013*
sTNFRI	0.229	0.109
sTNFRII	0.211	0.142
Clinics		
MEEM	0.223	0.120
NIHSS	-0.419	0.002*
Rankin	-0.332	0.019*

n: number of patients; DPM: Average Standard Deviation; ASPECTS: Alberta Stroke Program Early CT Score; BDNF: Brain Derived Neurotrophic Factor; VCAM-1: Vascular Cell Adhesion Molecule-1; VEGF: Vascular Endothelial Growth Factor; IL-1b: Interleukin-1 beta; sTNFR1: receptors of Tumor Necrosis Factors 1; sTNFRII: receptors of Tumor Necrosis Factors 2; MEEM: Mini-Mental State Examination; BAF: Frontal Assessment Battery; NIHSS: National Institutes of Health Stroke Scale; Rankin: Modified Rankin Scale; Statistical Test: *Spearman.

Table 5. Linear Multivariate Regression Analysis Between Alberta Stroke Program Early CT Score with Independent Variables Effectively Associated of Patients with Ischemic Stroke During Hospital Admission.

Variables	Coefficient B	p-value	95% confidence interval
Molecular			
Adiponectin	-1.504	0.005	0.000-0.000
Clinics			
NIHSS	-0.078	0.006	-0.132-0.023

NIHSS: National Institutes of Health Stroke Scale; Statistical test: *Linear multivariate regression analysis; Adjusted R coefficient=0.518.

CONCLUSION

Plasma levels of adiponectin are associated to the ASPECTS scores. Further studies must confirm this finding, evaluating the potential of this molecule as a prognostic biomarker after ischemic stroke.

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