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RELATIONSHIP BETWEEN C-REACTIVE PROTEIN AND CORTISOL WITH POST-STROKE DEPRESSION

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Abstract: Background: The occurrence of stroke is often related to vascular inflammation and accumulation of substances in the arterial walls. Depression is a common comorbidity, and changes in inflammatory biomarkers such as C-Reactive Protein (CRP) and Cortisol are found in patients with mood disorders. **Objective:** To relate the levels of CRP and cortisol with the occurrence of depression in individuals after ischemic stroke. **Method:** The study included 16 patients with post-acute ischemic stroke from the neurovascular unit of a public hospital in southern Brazil. Patients with BMI ≥ 30 and depression before stroke were excluded. The M.I.N.I was used to determinate the occurrence of depression after ischemic stroke event. Patients were allocated into two groups with and without depression. Hamilton Scale, Aphasic Depression Rating Scale (ADRS) were used for the assessment of psychiatric symptoms while Fugl Meyer (EFM), ADL Scale, Barthel Index, and Rankin Scale to assess motor dysfunctions. Assessment and blood were collected up to 90 days after the ischemic event. **Results:** Patients reported high levels of post-stroke depression (50% (n = 8)). The analysis of depressive symptoms showed a statistically significant difference with p=0.010. The CRP was found elevated in patients from both groups, Group 1, 37.5% (n = 3) and group 2, 50% (n = 4). The assessment of motor symptoms by Barthel showed a statistically significant difference with p=0.037. **Conclusion:** It was observed that the incidence of post-stroke depression is high in the sample studied. Patients with significant loss of motor capacity presented depressive symptoms without presence of depression. After analyzing the inflammatory biomarkers in the acute post-stroke phase, a significant increase in CRP was observed in both groups.

Keywords: Stroke; Post-Depression Stroke; Inflammatory Biomarkers.

INTRODUCTION

Cerebrovascular disease affects approximately 15 million people per year worldwide, making stroke the third leading cause of death in the adult population (PASCOE et al., 2011). Every year in the United States, about 795,000 people have strokes and 137,000 of those people die. Of the people having a stroke in any year, 185,000 have survived a stroke in the previous five years (TSAO et al., 2023). Several comorbidities arise after stroke, and depression is one of the most common, affecting approximately 33% of individuals who have suffered an ischemic event, being considered a risk factor for mortality (JIMÉNEZ et al., 2009; HOUSE et al., 2001). An important study of 103 patients demonstrated that half of post-stroke patients developed some mood disorder (ROBINSON et al., 1983). Another study carried out with 277 post-stroke individuals revealed that of these, 111 developed depression (POHJASVAARA et al., 1998). Some risk factors can be observed in the genesis of post-stroke depression, such as female individuals, smokers, diabetics, low education, and a history of pre-stroke depression (EVERSON et al., 1998). Two hypotheses are commonly described for the appearance of this comorbidity, the biological hypothesis, and the psychosocial hypothesis. The biological hypothesis concerns the area of brain injury, vascular microlesions, inflammatory cytokines and neurotransmitters as factors in the genesis of depression. The psychosocial hypothesis considers the psychological and social stress suffered by the individual after a stroke as the main factor in the occurrence of depression (FANG et al., 2009; SANTOS et al., 2009). However, neither of the two hypotheses was confirmed as an exclusive factor, with multifactorial aspects being described as the cause of post-stroke depression (SANTOS et al., 2009). Post-stroke depression has many negative aspects for the affected individual, caregivers, and society in general, and some medications with anti-inflammatory properties have been tested aiming to prevent post-stroke depression, without positive results (ASPLUND and ERIKSSON, 2011). Several studies have been carried out to determine whether depression can be considered an independent risk factor for a first stroke, and most of these studies have obtained positive results. Depressed individuals have increased levels of circulating cortisol and pro-inflammatory markers such as Interleukins 1 and 6 (IL-1, IL-6) and C-Reactive Protein (CRP), currently described as risk factors for stroke. Depressed individuals commonly exhibit unhealthy behaviors such as smoking, sedentary lifestyle, and poor diet, which are also reported as risk factors for stroke (JONAS and MUSSOLINO 2000; PAN et al., 2011; ARBELAEZ et al., 2007). Current studies show the influence of depression both as a risk factor for the occurrence of the first stroke and as a common post-stroke comorbidity. However, studies that investigate the processes that associate both pathologies are scarce. Cytokines and inflammatory biomarkers are the focus of some research involving the Central Nervous System (CNS), which aims to unravel the mechanisms between inflammatory processes and neurological pathologies (BRIETZKE et al., 2009; VAN EXEL et al., 2002; DOWLATI et al., 2010; HILES et al., 2012; BELZEAUX et al., 2010; KOIDO et al., 2010; BAUNE et al., 2012; DHABHAR et al., 2009; GUNNAR et al., 2012; MENZA et al., 2010). Among pro-inflammatory cytokines, the most frequently related to the CNS is IL-6 (GULOKSUZ et al., 2010; TRZONKOWSKI et al., 2004). Pro-inflammatory cytokines are extremely important in the immune response, acting as a defense against antigens, however, in patients 14 with vascular changes such as atherosclerosis, the prolonged action of such

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cytokines can be harmful (DOWLATI et al., 2010). Another substance that is commonly associated with inflammatory processes and the CNS is C-Reactive Protein (CRP) (HOPE et al., 2011; KOBROSLY and VAN WIJNGAARDEN, 2010). CRP is a protein produced in the liver, from the stimulation of inflammatory markers, mainly IL-6 (SINGH and NEWMAN, 2011; BRASIL et al 2007). Some important studies have reported the association between CRP and its precursor IL-6 with depression (WIUM-ANDERSEN et al., 2013; GIMENO et al., 2009). High CRP rates have been associated as a risk factor for the development of ischemic stroke (HASSIN-BAER et al., 2011; KUO et al., 2005).

In 2001, Rost and collaborators carried out a study with a 12-to-14-year follow-up of 1,462 healthy individuals and verified the occurrence of 196 ischemic events. Of these 196 events, they observed that patients had high CRP rates, proving its association with stroke. Recent studies have revealed that this protein acts not only as an inflammatory marker, but also participates in the genesis and progression of atherosclerosis (HOWREN et al., 2009; PAUL et al., 2004; CLEARFIELD, 2005). Torzewski in 1998, carried out a study where, through autopsy, in 15 bodies, he located CRP in all atherosclerotic plaques in coronary arteries. Therefore, it is important to verify the association between CRP and individuals with post-stroke depression, to better understand this mechanism, and so that preventive measures can be adopted.

Therefore, it is important to identify the levels of inflammatory markers, the presence of psychiatric disorders, and the influence of the occurrence of depression on functionality among individuals with and without post-stroke depression.

METHOD

Twenty-one patients after ischemic stroke from the Neurovascular unit of a public hospital in southern Brazil were invited to participate of the study; sixteen patients were included in the study. Patients with BMI ≥ 30 and depression before stroke were excluded (two patients had a BMI >30 and 3 had depression prior to the stroke). Patient Health Questionnaire (PHQ-9) was used to identify depression before stroke. Patients who scored equal to or greater than 5 were excluded. Ninety days after the ischemic event, patients were evaluated for psychiatric aspects, depressive episodes and functional performance. Soon after, blood was collected to evaluate inflammatory biomarkers. The M.I.N.I was used to determinate the occurrence of depression after ischemic stroke. Patients were allocated into two groups without and with depression. Hamilton Scale and Aphasic Depression Rating Scale (ADRS) were used to identify psychiatric symptoms. To assess patient's functionality Fugl Meyer (EFM), ADL Scale, Barthel Index, and Rankin Scale were applied. Approximately 10 ml of blood was collected through peripheral venipuncture from all patients and was stored in a tube with yellow cap gel (without anticoagulant). The blood was centrifuged for a period of 10 minutes, using speed of 4000 rotations per minute (400,000 g), at 4ºC. The supernatant material was stored in a freezer at -80ºC. The equipment used to analyze PCR and Cortisol was the Siemens Advia 1800. This study was approved by the Hospital of Clinics of Porto Alegre IRB under number 140017.

RESULTS

Sixteen patients who met the inclusion criteria and completed the assessments were allocated into 2 groups: Group 1 – Without Depression (n=8) and Group 2 – With Depression (n=8). The mean age in Group 1 was 63.8±9.4 and in Group 2 it was 55±16.77 with p=0.219. Group 1 was made up of 37.5% female individuals, while in Group 2 this percentage was 62.5% (p=0.619). Most patients in both groups are married (Group 1: 87.5% (n=7) and Group 2: 62.5% (n=5)).

To make up Groups 1 and 2, patients responded to the M.I.N.I., where the Depressive Episode was diagnosed. In Group 1, 100% (n=8) of patients did not meet the criteria for a Depressive Episode, both in the Current Depressive Episode and in the Recurrent Depressive Episode items. In Group 2, 7 patients met the Depressive Episode criterion through the M.I.N.I., of which 71.4% (n=5) met the criterion through the Current Depressive Episode item and 28.6% (n=2) met the criterion through the Recurrent Depressive Episode item. In Table 1, the groups are arranged according to the M.I.N.I. diagnostic criteria.

Variables	Group 1 Without Depression (n=8)	Group 2 With Depression (n=7)	p*
M.I.N.I. CDE			
Without criterion	8 (100%)	0 (0%)	0,07
With criterion	0 (0%)	5 (71,4%)	
M.I.N.I. EDR			
Without criterion	0 (0%)	0 (0%)	0,20
With criterion	0 (0%)	2 (28,6%)	

TABLE 1: Identification of the diagnostic criteria for depression by Mini International Neuropsychiatric Interview (M.I.N.I.).

(%): Frequency. Qui Square test.

Among the patients, only one was aphasic, and after applying the ADRS with the family member, the Depressive Episode was diagnosed, thus making up the 8th patient in Group 2 – With Depression. Using the M.I.N.I. instrument, other psychiatric disorders were diagnosed. In the item, Depressive Episode with Melancholic Features, 14.3% (n=1) met the diagnostic criteria, with p=0.467. In the Suicide Risk item, Group 1 was composed of 50% (n=4) of patients with no risk, 25% (n=2) low risk and 25% (n=2) high risk. In Group 2, 71.4% (n=5) of patients presented no risk and 28.6% (n=2) presented low risk, with no statistical difference between the groups (p=0.358). In the Hypomanic Episode item, in Group 1, 25% (n=2) of patients met the criteria, and in Group 2, 14.3% (n=1) met criteria for this disorder. In the items Agoraphobia without History of Current Panic and Current Social Phobia, 12.5% (n=1) of patients in Group 1 and 28.6% (n=2) in Group 2 met criteria in both items, however, without observe statistical difference (p=0.569). In the items Substance Dependence, Substance Abuse and Current Generalized Anxiety Disorder, 14.3% (n=1) of patients in Group 2 met criteria in each item. In the other disorders studied, no patient met the necessary criteria for diagnosis.

In table 2 the group without depression presented depressive symptoms despite not meeting criteria for a depressive episode according to the M.I.N.I., however, in group 2, higher scores were observed, demonstrating a depressive diagnosis. These findings were statistically significant (p≤0.037).

Variable	Group 1 Without Depression (n=8)	Group 2 With Depression (n=7)	p*
Hamilton	4 (2,25-11,0)	11,0 (9,0-17,0)	0,037*

TABLE 2: Scores of depressive symptoms in the groups.

(P25 a P75; Interquartil interval) and compared using Meann-Wvhittney test.

In the Fugl Meyer Scale, for upper limbs, the mean in Group 1 was 108.38±31.35 and in Group 2 it was 121.75±2.49 (p=0.249). For lower limbs, the mean in Group 1 was 90.38±13.83, and in Group 2, 96.88±4.67 (p=228). The mean total score of this instrument in Group 1 was 198.75±44.69 and in Group 2 it was 218.62±6.41 with p=0.234. In the Barthel Index instrument, Group 1 obtained scores with an average of 89.38±18.21, while Group 2, the average score was 95.62±5.63, with statistically significant results (p≤0.010). The performance of activities of daily living assessed by the ADL did not demonstrate a statistically significant difference between the groups (p=0.482) and showed that patients performed their daily activities independently. When assessing the presence of functional deficit using the Rankin scale, patients in both groups were classified as having no significant disability (p=0.609). Table 3 shows all the data obtained in the assessment of motor impairment in the groups studied.

Variables	Group 1 Without Depression (n=8)	Group 2 With Depression (n=8)	p*
Fugl Meyer (UL)	108,38±31,35	121,75±2,49	0,249
Fugl Meyer (LL)	90,38±13,83	96,88±4,67	0,228
Fugl Meyer (Total)	198,75±44,69	218,62±6,41	0,234
Barthel	89,38±18,21	95,62±5,63	0,010*
ADL	0 (0-4,0)	0 (0-0,75)	0,482
Rankin	1 (1,0-2,5)	1 (1,0-1,0)	0,609

TABLE 3: Performance of motor functionality in the groups.

Index of Daily Activities. Quantitative variables with symmetric distribution expressed as mean ± standard deviation and comparison using Student's t for independent samples. Median (P25 to P75; Interquartile range) and compared using the Meann-Wvhittney test.

CRP was above normal limits 37.5% (n=5) of patients in Group 1 and in Group 2, 50% (n=4) of patients had values above normal limits, however no statistically significant difference was observed between groups (p=0.401). In the analysis of the Cortisol biomarker, 100% (n=8) of patients had serum levels of the substance within normal limits. In Group 2, 87.5% (n=7) of patients presented values within normal limits (table 4).

Biomarkers	Group 1 Without Depression (n=8)	Group 2 With Depression (n=8)	p*
Cortisol *Normal*			
Below	8 (100%)	7 (87,5%)	
Above	0 (0%)	0 (0%)	0,401
	0 (0%)	1 (12,5%)	
C Reactive Protein			
Normal	5 (62,5%)	4 (50%)	0,817
Above	3 (37,5%)	4 (50%)	

TABLE 4: Analysis of inflammatory biomarker levels

(%): Frequency. Qui Square test

DISCUSSION

In this study, a high rate of patients who presented post-stroke depression was observed, 50% (n=8), which is consistent with important studies, which report a frequency of around 33% of this comorbidity (JIMÉNEZ et al., 2009; HOUSE et al., 2001).

According to Everson in 1998, there are some factors that are considered determinant for the development of post-stroke depression. Among these are the female sex, depression prior to the stroke, low education, smokers, and diabetics. In this follow-up, it was observed that all patients had low education levels, especially those allocated to Group 2. The average years of education in Group 1 was 6.12±2.10 years and in Group 2 it was 4.5±2. .83 years.

Through the M.I.N.I. Instrument, it is also

possible to observe other psychiatric disorders in addition to Depressive Episodes. Many of these disorders were found in patients from both groups, however, in depressed patients, a greater number of disorders were diagnosed (AMORIM, 2000). In the Suicide Risk item, patients without depression surprisingly presented higher scores, however, these patients are the ones who, despite not being diagnosed as depressed, presented higher scores for depressive symptoms.

Important studies highlight the increase in pro-inflammatory biomarkers in inflammation and attempt to understand the mechanism involved in depression and these biomarkers (DOWLATI et al., 2010; HOWREN et al., 2009; PAUL et al., 2004; CLEARFIELD, 2005).

In the present study, after analyzing the biomarkers CRP and Cortisol, we observed an increase in CRP in patients in both groups. This finding can be justified, since the total number of patients evaluated is still insufficient, and patients who are not depressed at the first evaluation may develop diagnosed depression over time. Furthermore, of the patients belonging to Group 1, 3 patients presented depressive symptoms, observed by the HAM-A instrument, without meeting criteria for diagnosis of depression by the MINI instrument. Furthermore, 3 patients belonging to Group 1 had elevated CRP, which suggests a relationship between the variables, depression, and CRP.

Regarding the analysis of the Cortisol substance, an increase was observed in only one patient, who was depressed and had the lowest scores in motor assessments. It is believed that, with a greater number of patients evaluated, and with the monitoring of these patients, we can accurately determine how important this variable is in the genesis of depression. In the present study, no changes in Cortisol values were observed, unlike findings in the literature. Such results may change with the inclusion of new patients in the study or, if this change does not occur, we can state that in the studied sample, this marker did not interfere with the analyzed objectives (JURUENA et al., 2004; MICHAEL et al., 1963; GIBBONS, 1964). The psychosocial hypothesis for the genesis of post-stroke depression believes that the psychological and social stress suffered by the individual would be mainly responsible for the occurrence of the comorbidity. Among the factors that lead to an increase in this stress, physical disability is an important variable, since patients with greater physical impairment tend to suffer greater tension when compared to patients who suffered a stroke and did not have physical sequelae. Furthermore, greater motor impairment has also been described as an agent in the genesis of post-stroke depression (TERRONI et al., 2003).

In general, patients with depression did not present significant motor deficits, unlike patients without depression who demonstrated reduced Barthel scores, showing greater functional dependence. Some authors use depressive symptom intensity scales to diagnose depression, other authors such as Ng et al., 1995 and Harney et al., 1993, used the DSM-III to diagnose depression, and the Hamilton Scale for symptom intensity depressive. In Harney's study, patients presented depressive symptoms in the first evaluation, and after 3 weeks, they had not yet developed a major depressive episode diagnosed by DSM-III, however, the reevaluation time was possibly too early to make the diagnosis. In Ng's study, after evaluating 52 patients, they concluded that the Hamilton Scale is an important instrument for evaluating the severity of depressive symptoms and progression to a depressive episode. It is believed that these patients may progress to a Depressive Episode diagnosed

through the M.I.N.I., since the depressive symptoms indicated by the Hamilton Scale are elements that together and, lasting for a certain time, or with increased intensity, characterize a Depressive Episode (FANG et al., 2009; SANTOS et al., 2009; HARNEY et al., 1993).

It was observed that the incidence of post-stroke depression is extremely high in the sample studied. Surprisingly, patients with significant loss of motor capacity were those belonging to the group of individuals without depression, however, these same patients presented depressive symptoms, suggesting the possibility of progressing to a Depressive Episode diagnosed through the M.I.N.I.. After analyzing the inflammatory biomarkers in the acute post-stroke phase, a significant increase in CRP was observed in both groups.

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