C-Reactive Protein and T3: New Prognostic Factors in Acute Ischemic Stroke

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Background: Several studies have shown that high level of plasma C-reactive protein (CRP) is associated with stroke outcomes and future vascular events, and a decrease in serum triiodothyronine (T3) was reported to be associated with stroke severity and poor prognosis. *Objective:* The goal of this study is to evaluate CRP and T3 as independent predictors of poor functional and cognitive outcomes in patients with acute ischemic stroke at hospital discharge. *Methods:* This study evaluated 120 patients who were admitted to the Clinical Hospital of Neurology and Psychiatry Brasov, between July 2016 and January 2017. The patients were evaluated for clinical stroke severity (National Institutes of Health Stroke Scale) and serum CRP and total T3 were evaluated on admission. Functional outcome and cognitive outcome were evaluated at discharge. *Results:* The severity of NIHHS scores were associated with higher CRP levels ($\beta = .583$, $P = .000$) and lower T3 concentration ($\beta = -.185$, $P = .043$). Poor cognitive prognosis was associated with CRP levels ($\beta = .441$, $P = .000$) but not with T3 concentrations ($P = .142$). Poor functional outcome was associated with higher CRP levels ($\beta = .457$, $P = .000$), but not with T3 concentrations ($P = .100$). Using CRP and T3 as prognostic factors resulted in a probability of 53.5% to predict a poor functional outcome and of 80.42% to predict a poor cognitive outcome in stroke patients at discharge. *Conclusions:* The study showed that higher CRP and lower T3 levels were associated with stroke severity on admission. Functional outcome is likely secondary to stroke severity but functional outcome at discharge was associated with higher CRP levels and not with T3 concentration. Cognitive outcome was associated with higher CRP levels and not with T3 concentration.

Key Words: Ischemic stroke—plasma C-reactive protein—triiodothyronine

Introduction

Ischemic stroke is among the leading causes of death and remains an important cause of handicap worldwide. According to epidemiological data, the impact of stroke on public health is steadily increasing due to the aging of the population, the increase in number of survivors after stroke, and myocardial infarction, therefore the population has a major risk of developing new vascular events. The annual mortality rate per 100,000 people from stroke in Romania has increased by 6.9% since 1990, with an average of 0.3% a year.[1,2]

Accurate and early appreciation of course and outcomes of the disease is decisive for identification of stroke patients who could benefit from targeted therapies in order to enhance recovery from stroke. Currently,

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ischemic stroke severity and prediction of functional and cognitive outcomes are evaluated using standardized clinical rating scales, patients' age, and extent on brain damage by imaging modalities. The prognostic value of commonly clinical parameters in stroke patients is quite subjective and insufficient, such that the identification of novel biomarkers that could potentially improve diagnostic accuracy of current outcome prognostication scales.[3]

Ischemic stroke is associated with systemic inflammatory response and increased serum concentrations of inflammatory biomarkers such as acute phase proteins, cytokines, and cell adhesion molecules.[4] C-reactive protein (CRP) is a proven biomarker of poor prognosis after stroke[5,6] and was associated with poor cognitive status in patients with cardiovascular disease.[7] Recent researches suggest that serum concentrations of thyroid hormones are altered in the acute phase of stroke.[8,9] Furthermore, proinflammatory cytokines are involved in the development of the low-T3 syndrome via inhibited central drive of hypothalamic-pituitary-thyroid-axis and impaired peripheral T3 production.[10] Few reports suggest that low T3 level can be an important prognostic biomarker of functional status in ischemic stroke patients.[11,12]

The goal of this study is to evaluate CRP and T3 as independent predictors of poor functional and cognitive outcomes at hospital discharge in patients with acute ischemic stroke.

Subjects and Methods

Study Design

In this study 321 patients were evaluated. They were admitted to the Clinical Hospital of Neurology and Psychiatry Brasov, between July 2016 and January 2017. After inclusion and exclusion criteria were applied, 120 patients with acute ischemic stroke were included in the study. A written informed consent was obtained from the patients or from their relatives on admission. Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours, documented by computer tomography scan indicating the presence of infarction and the absence of hemorrhage.[13]

Inclusion criteria were patient aged greater than or equal to 18 years with ischemic stroke confirmed by computer tomography scan. Exclusion criteria: hemorrhagic stroke, transient ischemic stroke, more than 24 hours from onset of symptoms in ischemic stroke patients, hepatic and renal failure, other causes associated with high CRP levels (infection, sepsis), known thyroid diseases, medication that could interfere with thyroid secretion (amiodarone, lithium) or could influence the binding of thyroid hormones to plasma proteins at therapeutic doses (furosemide, carbamazepine).

Study Protocol and Data Collection

Every patient was subjected to a detailed clinical history and neurological examination. Stroke severity on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS), and the distribution of NIHSS scores was classified into three categories: mild for NIHSS less than 8; moderate for NIHSS 8−14; and severe for NIHSS greater than 14.[14] We divided the patients into 3 groups according to the 3 categories of NIHSS score. TOAST classify (Trial of Org 10172 in Acute Stroke Treatment) was used to evaluate the etiology of stroke: large artery atherosclerosis, cardioembolic, small-vessel occlusion (lacunar), undetermined or other etiology. We used Oxford Community Stroke Project classification (also known as the Bamford or Oxford classification) based on extent of the symptoms, as follows: total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct, and lacunar infarct. At discharge we used The Mini-Mental State Examination (MMSE) to measure the cognitive impairment. Two patients were excluded because of severe disturbances in communication. We used a cut-off score of 24, with a good cognitive outcome at a MMSE score higher than 24 and a poor cognitive outcome MMSE score equal to or lower than 24. For measuring the degree of disability or dependence we used modified Rankin Scale (mRS). We studied the relation between CRP and T3 values and poor functional outcome at discharge defined as mRS score greater than 3.

Baseline characteristics including demographic data, stroke risk factors—hyperlipidemia, hypertension, diabetes mellitus, transient ischemic attacks, coronary artery disease, atrial fibrillation, smoking, alcohol consumption were investigated. Cerebrovascular risk factors were described, such as current or previous cigarette smoking; alcohol abuse (100 g/day); hypercholesterolemia (treatment of hypercholesterolemia and/or fasting total cholesterol level > 200 mg/dL); hypertriglyceridemia (treatment of hypertriglyceridemia and/or fasting triglycerides level > 150 mg/dL); arterial hypertension (history of hypertension and/or systolic blood pressure greater than or equal to 130 mm Hg and/or diastolic pressure greater than or equal to 90 mm Hg, treated or not); history of diabetes mellitus or new diagnosis (two fasting plasma glucose level greater than or equal to126 mg/dL (7.0 mmol/L), or plasma glucose greater than or equal to 11.1 mmol/L (200 mg/dL) 2 hours after a 75 g oral glucose intake as in a glucose tolerance test or symptoms of high blood sugar and casual plasma glucose greater than or equal to11.1 mmol/L (200 mg/dL) or glycated hemoglobin (HbA1C) greater than or equal to 6.5.[15] Obesity was defined as body mass index (BMI) greater than or equal to 30 kg/m^2. Cardiovascular comorbidities such as arrhythmias were documented by standard 12-lead electrocardiogram (ECG), and selected causes were diagnosed

by echocardiography. On admission we performed a large panel of routine blood count, red blood cell count, white blood cell count, platelets, fasting plasma glucose, lipid profile, uric acid, total calcium, and other laboratory parameters were measured. Blood samples for Thyroid stimulating hormone (thyrotropin) (TSH), total T3, CRP were taken at the time of admission and then were centrifuged and serum was stored frozen at −40°C. After the study completion, samples from all the patients were analyzed in a single batch. Blood samples were analyzed using immunoturbidimetric method for CRP, and chemiluminescent microparticle immunoassay for TSH and T3 (Abbott Architect ci8200 biochemistry analyzer). Normal values of CRP range from 0.5 to 5 mg/dL. Normal ranges for TSH were 0.35-4.94 mUI/L and for total T3 0.89-2.44 nmol/L. Patients who had low TSH levels with or without high T3 levels were considered as belonging to the hyperthyroid pattern while patients who had high TSH with or without T3 were considered as belonging to the hypothyroid pattern. Patient who had low T3 levels and normal or low TSH levels were considered as having sick euthyroid syndrome.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 for Windows. Values for CRP, T3, and TSH showed a non-normal distributed pattern according to the Kolmogorov−Smirnov test and were log transformed and consequently Mann−Whitney test were further applied. Independent-sample t tests were performed for variables with normal distribution. Categorical data were presented as percentage and continuous data as mean ± standard deviation. Receiver operating characteristic (ROC) curves were calculated to define the best cut-off value of CRP and T3 to predict outcomes. The accuracy of the test was assessed measuring the area under the ROC curve (AUROC). We investigated the associations of stroke severity on admission (NIHSS score), functional outcome (mRS) and cognitive assessment (MMSE) at discharge with levels of CRP and T3 by performing Spearman's correlation. Subsequently, by performing bivariate linear regression analyses we evaluated the association of severity of stroke, mRS, and MMSE with concentrations of CRP and T3, age, and gender. Results were presented as β (P value). Then, we explored the risk for severe NIHSS score, poor mRS, and MMSE scores associated with CRP and T3 by performing univariate binary logistic regression analyses. Results were presented as odds ratios (95% confidence interval). Finally, we evaluated the independent association of stroke severity, poor functional and cognitive outcomes with T3 and CRP concentrations by performing multivariate regression analyses adjusting for factors that were associated with stroke severity in previous univariate analyses. P values less than .05 were considered statistically significant.

Results

On analysis of the age and sex distribution of the study population, it was found that the mean age was 68.8 ± 10.08 years, with age ranged between 47 and 94 years. More than half of patients were male (51.67%) and 71.67% were from urban environment. Sixty-five (54.16%) patients had atherothrombotic stroke, 32 (26.67%) small-vessel occlusive stroke, 17 (14.16%) cardioembolic stroke, and in 6 (5%) patients the diagnosis was other/uncertain cause of stroke. The demographic characteristics, cardiovascular risk factors, CRP, and T3 levels are presented in Table 1.

Stroke severity evaluated with NIHSS score revealed a mean score of 9.78 ± 3.97, with 32 patients (26.67%) stratified as mild NIHSS, 65 patients (54.16 %) as moderate NIHSS, and 23 patients (19.16%) as severe NIHSS. The severe NIHSS score was more frequent in women 60.87% compared with 39.13% in men. Based on subtype of stroke from TOAST classification, it was revealed that 18.46% of large-artery atherosclerosis stroke patients, 47.05% of those with cardioembolic stroke, and 6.25% of those with small-artery occlusion stroke present with severe NIHSS score (Table 1). Risk factors for stroke as atrial fibrillation (17.39%) and diabetes type 2 noninsulin dependent (43.48%) were found to be more frequently associated with severe NIHSS score.

There was observed a positive correlation of severity of stroke with CRP levels (r = .698, P = .000) and a negative correlation with T3 concentrations (r = −.206, P = .024). Univariate linear regression analyses revealed that severity of NIHHS scores was associated with higher CRP concentration (β = .583, P = .000) and lower T3 concentration (β = −.185, P = .043). Binary logistic regression analyses showed that CRP levels (odds ratio [OR] = 1.33; 95% confidence interval [CI] {1.15-1.54}, P = .000), but not T3 concentrations (OR = .538; 95% CI [0.149-1.95], P = .346), were associated with severity of NIHSS score at admission. In multivariate regression analyses the worse NIHSS score remained independently associated only with higher CRP levels (β = .583, P = .000). High CRP levels were reported in all stroke subtypes, mean values of CRP were significantly higher in cardioembolic stroke (25.69 ± 32.4 mg/dL) followed by atherothrombotic large vessels (14.34 ± 23.9 mg/dL) and lacunar stroke (7.4 ± 10.76 mg/dL) (Table 2).

The mean length of hospitalization was 9.59 ± 3.13 days. Mean MMSE score at discharge was 16.86 ± 7.67, 74.16% of patients having a score less than or equal to 24 (Table 3). A negative correlation of MMSE score with CRP levels (r = −.517, P = .000) and a positive correlation with T3 concentrations (r = .196, P = .032) were observed. In univariate linear regression analysis, the poor cognitive prognosis was associated with CRP levels (β = .441, P = .000) but not with T3 concentrations (P = .142). At discharge the mean mRS was 3.15 ± 0.99, 30.83% of patients having a score greater than 3 (Table 3).

Table 1. *Demographic characteristics, cardiovascular risk factors, CRP, and T3 levels*

Characteristics of ischemic stroke patients	Mild NIHSS		Moderate NIHSS		Severe NIHSS		*P* value
	n	%	N	%	N	%	
Total (n = 120)	32	26.67%	65	54.16%	23	19.16%	.000
Male	16	50%	33	50.77%	9	39.13%	.135
Female	16	50%	32	49.23%	14	60.87%	
Median age (±SD)	65.5 (±9.88)	70 (±9.77)	69 (±10.51)	.810			
Environment							
Rural	9	28.13%	18	27.7%	7	30.43%	.931
Urban	23	71.87%	47	72.3%	16	69.57%	
History of ischemic stroke	6	18.75%	9	13.84%	5	21.74%	.417
Cigarette smoking	14	43.75%	42	64.62%	11	47.83%	.168
Alcohol abuse	14	43.75%	26	40%	5	21.74%	.230
Hypertension							
Grade 1	3	9.37%	6	9.23%	2	8.7%	.810
Grade 2	16	50%	23	35.38%	7	30.4%	
Grade 3	10	31.25%	25	38.46%	12	52.17%	
Atrial fibrillation	4	12.5%	9	13.84%	4	17.39%	.867
Obesity	7	21.88%	21	32.3%	8	34.78%	**.000**
Hypercholesterolemia	7	21.88%	30	46.15%	4	17.39%	**.008**
Hypertriglyceridemia	3	9.37%	24	36.93%	5	21.74%	.234
Disturbances of carbohydrate metabolism							
Impaired glucose tolerance	9	28.13%	18	27.7%	4	17.39%	.500
Type 2 noninsulin requiring diabetes mellitus	6	18.75%	17	26.15%	10	43.48%	.076
Type 2 insulin requiring diabetes mellitus	1	3.12%	4	6.15%	1	4.34%	.717
Laboratory results							
T3 (nmol/L) (±SD)	1.17 (±.25)	1.18 (±.32)	1.04 (±.27)	**.012**			
CRP (mg/dL) (±SD)	1.59 (±1.33)	13.09 (±19.28)	32.6 (±33.43)	**.000**			
Stroke subtypes							
Large-artery atherosclerosis	13	20%	40	61.54%	12	18.46%	**.010**
Cardioembolism	3	17.65%	6	35.3%	8	47.05%	
Small-artery occlusion	12	37.5%	18	56.25%	2	6.25%	
Other determined	1	100%	0	0%	0	0%	
Undetermined	3	60%	1	20%	1	20%	

Bold values indicate that they are statistically significant.

Abbreviations: CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation;T3, triiodothyronine.

Table 2. *Distribution of CRP and T3 mean values in various subtypes of stroke*

	LAA	CE	SAA	UN	*P*
CRP (mg/dL) (mean ± SD)	14.34 (±23.9)	25.69 (±32.4)	7.4 (±10.76)	7.7 (±8.86)	.058
T3 (nmol/L) (mean ± SD)	1.13 (±.28)	1.10 (±.37)	1.22 (±.28)	1.15 (±.21)	.527

Abbreviations: CRP, C-reactive protein; CE, cardioembolic; LAA, large artery atherosclerosis; SAA, small artery atherosclerosis; T3, triiodothyronine; UN, undetermined etiology.

We found that poor functional outcome at discharge using mRS was positively correlated with serum CRP level (r = .392, $P = .000$) and negatively with T3 concentrations (r = −.193, $P = .034$) on admission. Poor functional outcome at discharge was associated with higher CRP levels on admission ($\beta = .457$, $P = .000$), but not with T3 concentrations ($P = .100$). In binary logistic regression analyses, higher CRP concentrations on admission were not associated with increased risk for poor functional outcomes (OR = 1.035; 95% CI [0.996-1.076], $P = .080$) but were associated with poor cognitive outcomes (OR = .608; 95% CI [0.467-0.790], $P = .000$) at discharge. Lower free T3 concentrations on admission were associated neither with increased risk for poor cognitive outcomes (OR 1.433; 95% CI [0.271-7.590], $P = .672$) nor for functional outcomes at discharge (OR = .769; 95% CI [0.181-3,261], $P = .722$).

Using ROC curve analysis, we detected a cut-off level of serum CRP on admission of 3.035 mg/dL to predict a high severity of stroke with a sensitivity of 79.7% and a specificity of 75.6% (area under the ROC curve [AUROC] = .860), a poor cognitive prognosis using MMSE with a sensitivity of 75.6% and a specificity of 83.3% (AUROC = .748) and a poor functional prognosis using mRS with a sensitivity of 83.8% and a specificity of 49.4% (AUROC = .864). A cut-off value for T3 of 1.115 nmol/L on admission was observed to predict the severity of stroke with a sensitivity of 58.2% and a specificity of 58.5% (AUROC = .526), a poor cognitive prognosis with a sensitivity of 66.7% and a specificity of 58.9% (AUROC = .633) and a poor functional outcome with a sensitivity of 70.5% and a specificity of 55.4% (AUROC = .614). In likelihood ratio analysis, using together CRP and T3 levels as prognostic factors, resulted a probability of 53.5% to predict a poor functional outcome and a probability of 80.42% to predict a poor cognitive outcome in stroke patients at discharge.

Table 3. *Cognitive and functional outcomes*

Mini mental state examination (n = 118)	
Mean MMSE score	16.87 ± 7.66
Poor cognitive outcome (score ≤ 24)	74.16%
Modified Rankin scale (mRS) (n = 120)	
Mean mRS	3.15 ± .99
Poor functional outcome (score > 3)	30.8%

Discussion

Stroke is the first leading cause of disability and third most common cause of death in developed country.[16] CRP is a predictor of cerebrovascular disease and peripheral vascular disease as well as of sudden death. Thus, CRP as inflammatory marker has attracted clinical attention as a predictive marker of ischemic stroke. Experimental data demonstrate that acute inflammation reaction in response to cerebral ischemia would occur within the first 2 hours from onset.[17] However, data are limited in terms of the time course of acute phase responses in humans. Montaner et al.[18] described a peak of IL-6 at 24 hours after the onset of symptoms. Di Napoli[19] described a rise in CRP within 3 hours after stroke compared to status of pre-stroke. Analysis of a subgroup from a prospective observational study concluded that CRP levels greater than 1.01 mg/dL were associated with an unfavorable prognosis. Di Napoli et al.[20] studied within 1 year the prognostic influence of CRP measured within 24 hours after ischemic stroke and described an association between elevated CRP levels and unfavorable prognosis. In our study we demonstrated with statistical significance ($P < .05$) the association between high levels of CRP and stroke severity evaluated with NIHSS score and poor cognitive and functional outcomes at discharge. A serum level CRP of 3.035 mg/dL on admission predict a higher severity of stroke with a sensitivity of 79.7% and a specificity of 75.6%, a poorer cognitive outcome with a sensitivity of 75.6% and a specificity of 83.3%, and a poorer functional outcome with a sensitivity of 83.8% and a specificity of 49.4%. These results confirm that high level of CRP can be used as a prognostic indicator in ischemic stroke.

Other studies reported significant elevations of CRP levels in patients with cardioembolic stroke.[21,22] In our study we also observed the highest level of CRP in cardioembolic stroke subtype followed by atherothrombotic large vessels. In several studies high level of CRP has been associated with poorer outcomes in instable angina, myocardial infarction.[23] Inflammatory reaction contributes to secondary neuronal injury after stroke.[24,25] Levels of CRP were high in acute phase of stroke and this persists high in survivors of stroke.[26] Progression of vascular disease could occur because a chronic inflammatory state may persist after the acute phase of stroke.

Multiple neuroendocrine modifications that have been described after stroke either have an adaptive role or are

considered dysfunctions of the endocrine system. Stroke induces a systemic inflammatory reaction in which proinflammatory cytokines play an important role in the occurrence of low-T3 syndrome by inhibition of central drive of hypothalamic-pituitary-thyroid-axis and impaired peripheral T3 production.[3] Low-T3 syndrome is frequently noticed in critically ill patients who have nonthyroidal illness syndrome. There are some evidences which suggest that thyroid hormones are neuroprotective in the context of ischemic stroke and lower serum concentrations of T3 are associated with greater mortality and handicap rate of stroke patients.[8,11] However, data regarding the association between T3 levels and functional outcomes after stroke are conflicting. Several studies suggest that low T3 levels in acute ischemic stroke are associated with greater stroke severity and higher mortality rates.[11,27] According to a retrospective study who reviewed 1072 ischemic stroke patients, low T3 concentration was an independent predictor of poor functional outcome.[28] In a study of Neidert et al.[27] it was reported that lower total T3 concentrations on admission were related to worse functional outcomes 90 days and 1 year after ischemic stroke, but in multivariate analyses total T3 concentrations not independently predicted worse outcomes. In our study we observed that lower T3 concentration were statistically associated only with severity of NIHSS scores but not with worse functional and cognitive outcomes. Though prior studies have demonstrated an association between low T3 levels and poor outcomes, it is likely that this study was underpowered to detect an association. However, dosing of CRP and total T3 concentrations may be used to predict severe course in ischemic stroke patients. Our study resulted in a probability of 53.5% to predict a poor functional outcome and of 80.42% to predict a poor cognitive outcome in stroke patients at discharge.

The validity of our results has several limitations: a small group of patients enrolled in the study and rather few patients with severe stroke were included, a single determination of T3 and CRP without dynamic evaluation may not reflect the status of the patients during the acute phase, we could not reevaluate patients after discharge. Statistical power may be insufficient to draw conclusion, larger studies must be done to confirm our conclusion.

Conclusions

Higher levels of CRP and lower T3 concentrations were associated with clinical severity of stroke on admission. Poor cognitive and functional outcomes at discharge were associated with high CRP levels but not with T3 concentrations. A better understanding of inflammatory factors and neuroendocrine response in acute ischemic stroke and implicitly classifying poststroke patients into relatively high risk and low risk groups based of CRP and T3 levels may help to define and predict functional and cognitive outcomes.

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