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Research Article

Can C-Reactive Protein and T3 be Predictive for Prognosis in Ischaemic Stroke?

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Abstract

Background: Some studies have shown that elevated plasma C-reactive protein (CRP) levels in acute ischaemic stroke are associated with stroke severity and early prognosis while low serum triiodothyronine (T3) levels are associated with poor prognosis. The aim of this study is to evaluate whether serum CRP and T3 are independent predictors of stroke severity and early prognosis in patients with acute ischaemic stroke.

Material and Method: A total of 716 patients hospitalized with the diagnosis of acute ischaemic stroke were included in the study. The patients did not have any known infectious or thyroid diseases. NIHSS score was used to evaluate clinical stroke severity and patients were grouped as mild (<8), moderate (8-14) and severe (> 14) stroke. Modified Rankin Score was used on the 10th day to evaluate early prognosis and patients were grouped as good prognosis (mRS:0-2) and poor prognosis (mRS:3-6). The relationship between serum CRP and free T3 levels and stroke severity and early prognosis were investigated.

Results: There was a significant difference in CRP and T3 levels (p:0.007 and p:0.01, respectively) according to stroke severity. Higher NIHHS scores were correlated with higher

CRP levels (rho=.283, p = 0.001) and lower T3 levels (rho= -.188, p = 0.001). Patients with poor functional outcomes had high CRP levels (rho=.110, p = 0.01) and low T3 levels (rho= -.184, p = 0.001)

Conclusion: Statistically significant relationship between stroke severity and early prognosis and CRP and T3 levels in patients with acute ischaemic stroke suggests that CRP and T3 levels may be a predictor of prognosis in acute ischaemic stroke.

Keywords: Acute Ischaemic Stroke; C-reactive Protein; T3

Introduction

Acute ischaemic stroke (AIS) is the most common type of all stroke syndromes [1]. Ischaemic stroke symptom severity is evaluated using standardized clinical stroke symptom severity rating scales (e.g. National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), patients' age and extent of brain damage on routinely available imaging modalities. These are the most commonly employed clinical variables to predict short and long-term ischaemic stroke patient outcomes [2,3]. However, the prognostic value of this clinical parameters remains insufficient and there is a necessity of new blood biomarkers that could potentially improve the diagnostic accuracy of stroke severity and prognosis [2,4,5]. Two of the suggested biomarkers are serum C-reactive protein (CRP) and triiodothyronine (T3). Ischaemic stroke is associated with systemic inflammatory response and increased serum concentrations of inflammatory biomarkers such as C-reactive protein (CRP). Higher CRP concentrations have been documented as a reliable biomarker of poor prognosis in patients with ischaemic stroke [5-7]. A study of 561 ischaemic stroke patients has demonstrated that patients with CRP concentrations of ≥7 mg/L within 12 hours

of symptom onset had increased risk of poor functional outcomes and death at 3 months, relative to patients with CRP concentrations of <7mg/L [7]. Inflammatory response can interfere with normal functioning of the hypothalamo-pituitary-thyroid (HPT) axis. It has been demonstrated that inflammatory cytokines may cause reduction of serum T3 concentrations by inhibition of central control of the HPT and by interfering with normal functioning of the 5'-deiodinase enzymes that are mainly responsible for T4 to T3 conversion in peripheral tissues [8,9].

Many studies suggest that serum concentrations of the HPT hormones are altered in patients suffering from stroke [10-12]. Thyroid hormones undergo complex metabolism in peripheral tissues, including the brain. It is well described that normal functioning of the HPT is commonly disturbed in severely ill patients and is associated with reduced serum T3 concentrations and normal TSH [11]. Some evidence in animal models suggests that thyroid hormones are neuro-protective and some studies hypothesized that in the case of ischaemic brain damage, lower serum concentrations of T3 and T4 are associated with reduced survival and increased disability [10,13,14]. Clinical studies in ischaemic stroke patients have shown that lower serum concentrations of T3 and T4 in acute phase of stroke was associated with more neuronal damage and reduced survival and increased disability [13-16]. These findings suggest that low T3 syndrome can be an important prognostic biomarker of functional outcomes in ischaemic stroke patients.

The aim of the present study was to evaluate the association of serum CRP and T3 levels with clinical stroke severity and early prognosis of patients diagnosed with AIS.

Material and Methods

Patients of a total of 716 in number with a diagnosis of acute ischaemic stroke and hospitalized in the Neurology Department between January 2016 and January 2018 were included in the study. The patients or their relatives signed in a written informed consent on admission. This study has been conducted in agreement with the Helsinki Declaration. The definition of cerebral infarction was a focal neurological deficit with a sudden onset that continued beyond 24 hours, documented by diffusion magnetic resonance imaging (MRI) scan. Patients aged greater than 18 years, whose ischaemic strokes were confirmed by diffusion MRI scan and admitted in the first 24 hours of the stroke were included in the study. Patients with hemorrhagic stroke, venous sinus thrombosis, venous or hemorrhagic infarct, hepatic and renal failure and other causes associated with high CRP levels like infection, inflammatory or rheumatological disease, any known history of thyroid diseases, medications that may influence thyroid metabolism and whose blood samples were taken after 24 hours of the initiation of stroke were excluded from the study.

The National Institutes of Health Stroke Scale (NIHSS) was used to assess stroke severity on admission. The results of the NIHSS scores were grouped into three categories as: mild for NIHSS less than 8; moderate for NIHSS 8-14; and severe for NIHSS greater than 14. Modified Rankin score (mRS) was used to evaluate early stage prognosis and two groups were formed according to the scores on the 10th day: good prognosis (mRS:0-2) and poor prognosis (mRS:3-6).

CRP and T3 levels in the first 24 hours of ischemic stroke were examined in mild, moderate and severe stroke severity groups. Also in the prognosis groups according to mRS, CRP and T3 levels were examined. Any correlation between serum levels of CRP and T3 and the stroke severity on admission and the prognosis at the 10^{th} day of the stroke was investigated.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 17 was used for statistical analysis. The Kolmogorov-Smirnov test showed a non-normal distributed pattern for CRP and T3 values and the values were log transformed and consequently Mann-Whitney U test was 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. Spearman's correlation was performed to investigate the associations of stroke severity on admission (NIHSS score) and functional outcome (mRS) with levels of CRP and T3.

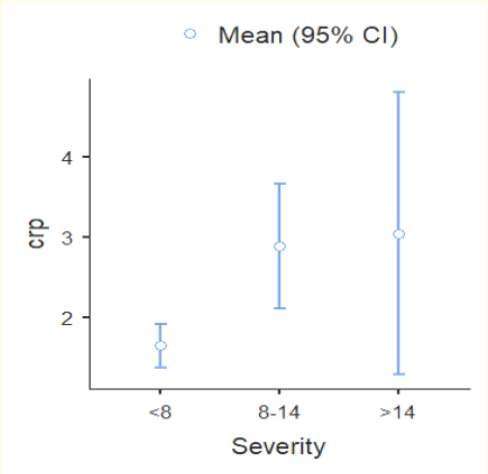
Results

A total of 795 patients with acute ischemic stroke was investigated and as 79 patients were not suitable for the inclusion criteria 716 patients were studied. The mean age of the patients was 69.2 ± 12.9. There were 345 female patients (%48) with a mean age of 71 ± 12.5 and 371 male patients (%51) with a mean age of 66.6 ± 12.7. 103 of the patients were under age of 55 and 613 patients were older than 55 years of age.

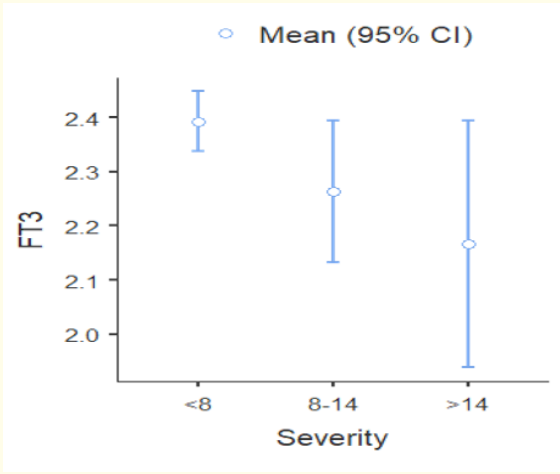
According to the NIHSS there were 416 patients in the mild group, 99 patients and the moderate group and 25 in the severe group. The mean CRP in mild, moderate and severe groups were 1.7 ± 3.1mg/dL, 2.7 ± 3.3 mg/dL and 3.04 ± 4.2 mg/dL, respectively. The mean free T3 levels in mild, moderate and severe groups were 2.4 ± 0.4nmol/L, 2.2 ± 0.5 nmol/L, and 2.1 ± 0.5 nmol/L, respectively. There was a significant difference in CRP and T3 levels ($p < 0.001$ and $p = 0.003$, respectively) according to NIHSS scores (Table 1). The severity of NIHHS scores were correlated with higher CRP (rho = .283, p = 0.001) and lower T3 (rho = -.188, p = 0.000) levels (Table 3, Graphic 1,2).

Variables	Mild NIHSS N:416	Moderate NIHSS N: 99	Severe NIHSS N: 25	*p*-value
Age [years]	65.5 ± 10.88	71 ± 9.47	68 ± 10.41	0.720
Gender				
Female (n)	245	81	19	
Male (n)	309	46	16	
CRP (mg/dL) (± SD)	1.7 ± 3.1	2.7 ± 3.3	3.04 ± 4.2	<0.001[a]*
Median	0.7	1.8	1.6	
Minumum	0.01	0.01	0.1	
Maximum	25	25.4	17.1	
T3 (nmol/L) (± SD)	2.4 ± 0.4	2.2 ± 0.58	2.1 ± 0.52	0.003[a]*
Median	2.4	2.2	2.1	
Minumum	0.9	1.2	1.1	
Maximum	3.7	5.6	3.1	

Table 1: Demographic characteristics, CRP, and T3 levels according to stroke severity. (SD: Standard Deviation, a: Kruskal-Wallis). *statistically significant.



Graphic 1: Serum CRP levels in stroke severity groups



Graphic 2: Serum FT3 levels in stroke severity groups.

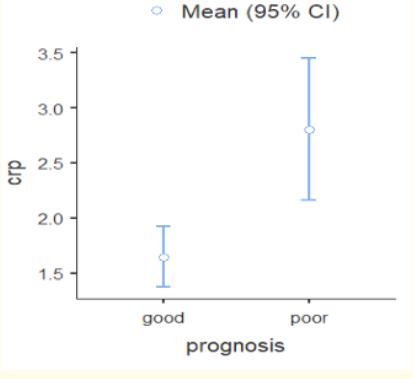
There were 524 patients (%75.9) in the good prognosis group and 166 (%24.1) in the poor prognosis group. The mean mRS average was 1.9 ± 1.5. In the good prognosis group CRP levels were 1.6 ± 3.05 mg/dL and 2.8 ± 3.8 mg/dL in the poor prognosis group. There was a significant difference between these two prognostic groups in terms of mean CRP levels and mean T3 levels (2.4 ± 0.4 nmol/L, 2.1 ± 0.5 nmol/L) according to early prognosis ($p < 0.001$ and $p < 0.001$, respectively) (Table 2). Higher CRP levels (rho = .110, P =0.01) and low T3 levels (rho = -.184, P = 0.000) were correlated with poor functional outcomes (Table 3, Graphic 3,4)

		CRP	Free T3
NIHHS severity	Spearman's rho	.283	-.188
	p-value	0.001	0.001
mRS	Spearman's rho	.110	-.184
	p-value	0.01	0.001

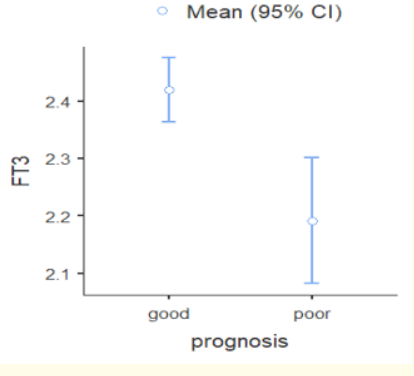
Table 3: Correlation between stroke severity and prognosis with CRP and T3 levels.

	Good prognosis (mRS 0-2) N:524	Poor prognosis mRS (3-6) N:166	p
Age [years]	67.5 ± 13.03	73.4 ± 12	<0.001[a]*
Median	68	76	
Minimum	31	32	
Maximum	96	94	
Gender			<0.001[b]*
Female (n)	223	104	
Male (n)	301	62	
CRP (mg/dL) (± SD)	1.6 ± 3.05	2.8 ± 3.8	<0.001[a]*
Median	0.7	1.4	
Minimum	0.001	0.01	
Maximum	25	26	
T3 (nmol/L) (± SD)	2.4 ± 0.4	2.1 ± 0.5	<0.001[a]*
Median	2.4	2.1	
Minimum	0.9	1.09	
Maximum	3.7	5.6	

Table 2: CRP and T3 levels according to prognosis.
(a: Mann-Whitney U, b: Chi Square) * statistically significant



Graphic 3: Serum CRP levels in prognostic groups.



Graphic 4: Serum FT3 levels in prognostic groups.

Discussion

CRP is a well-known inflammatory marker. It has been shown in laboratory studies that an acute inflammatory reaction occurs within the first few hours of a cerebral infarction. This information led to the idea that CRP may play a significant role as a predictive marker of ischaemic stroke [17]. CRP has been shown to have increased within the first 3 hours after stroke in some studies [18]. Furthermore, studies have shown that there exists a relationship between CRP and prognosis such that elevated CRP levels in acute term indicate a worse prognosis [19,20]. Our study demonstrated that there exists a statistically significant ($P < 0.05$) association between high levels of CRP and stroke severity evaluated with NIHSS score and worseearly term functional outcomes evaluated with mRS (between scores 3-6) at discharge. Our results confirm that a high level of CRP can be a determinant of worse prognosis in ischaemic stroke and this relationship can be explained with the degree of inflammation secondary to neuronal injury in acute ischaemic stroke patients [21]. High levels of CRP are supposed to persist for up to 3 months in survivors of AIS [22].

The fact that systemic inflammatory reaction and the related cytokines bring about a low-T3 syndrome by inhibiting the HPT-axis and impairing peripheral T3 production [10]. Some studies have suggested clues that thyroid hormones may have neuroprotective roles in ischaemic stroke, and therefore lower serum concentrations of T3 were found to be associated with increased mortality and morbidity inacute ischaemic stroke patients [13,16]. It has been shown in several studies that low T3 levels in AIS are related to more severe levels of stroke and higher mortality rates [16,23]. A retrospective study of 1072 ischaemic stroke patients demonstrated that low T3 levels was an independent prognostic indicator of worse functional outcome [23]. In our study, a statistically significant association ($p < 0.05$) of lower T3 concentrations with high NIHSS scores (more severe stroke) and with worse early term functional outcomes evaluated with mRS (scores 3-6) was observed. Even though our findings were in accordance with prior studies by means of stroke severity and early functional outcomes, the validity of our results has some limitations; the most important of which was a single determination of CRP and T3 without knowledge of the values before the stroke. Another less important limitation was not following the long-term prognosis of the patients.

Conclusions

It has been depicted that higher levels of CRP and lower T3 concentrations in patients with acute ischaemic stroke on admission were found to be associated with more severe stroke and worse early prognosis in our study. A better understanding of inflammatory factors and neuroendocrine response in AIS may help to define and predict functional outcomes.

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