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Association of Serum Levels of Pentraxin-3, M-ficolin, and Surfactant Protein A with the Severity of Ischemic Stroke

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ABSTRACT

Stroke is one of the most leading causes of death and disability in the world. Complement system activation contributes to pathogenesis and neuronal damage following stroke. There are no defined biological serum markers to determine the severity of stroke in acute phases. The purpose of current study was to determine the association of three complement activators, namely Pentraxin-3 (PTX3), M-ficolin, and Surfactant protein A (SPA) with the severity of ischemic stroke.

This cross-sectional study was done on 82 patients diagnosed with ischemic stroke at 24-96 hours of initiation of the clinical symptoms during 2014-2015. The serum levels of PTX3, M-ficolin, and SPA were measured by enzyme-linked immunosorbent assay (ELISA). The patients were divided in three stroke severity groups according to modified National Institute of Health Stroke Scale mNIHSS.

The results showed that the more severity of the stroke was, the higher serum levels of three evaluated molecules ($p<0.001$) were. The correlation of serum level of PTX3, M-ficolin, and SPA with stroke severity was 0.732, 0.736, and 0.731, respectively.

There is a strong association between serum levels of PTX3, M-ficolin, and SPA with the severity of ischemic stroke. Clinically, such association may be considered to evaluate the severity of the ischemic stroke.

Keywords: Ischemic stroke; Pentraxin-3, M-ficolin; Surfactant protein A

INTRODUCTION

Stroke is one of the most leading causes of disability and mortality in the world.[1] The complement, cascade is an effector arm of innate immune system which is activated via three main pathways, namely alternative, classic, and mannose-binding lectin (MBL). The latter is importantly activated in the pathogenesis of the ischemic stroke.[2] Multiple activators of complement are present in injured tissue and contribute to the release of inflammatory mediators, opsonophagocytosis, killing of pathogens, and removal of damaged host cells.[2] Recently some clinical studies

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provided evidence supporting activation of complement cascade in acute ischemic stroke[2-4] that contributed in larger brain infarction and worsening of neurological deficits.[2,5-7] Depletion of complement system in some rodent and human studies has been considered as a therapeutic target[8] that could improve outcome, neurologic deficit, and infarct size of the stroke.[2,6,9]

Many studies evaluating the association of complement and stroke, have shown the alteration of different complement markers such as c3, c4, [4, 5, 10-12] C-reactive protein (CRP),[3,13] C1q and C1q inhibitor (c1q INH),[9,12,14,15] and MBL[2,4] after stroke. Recently, some studies have investigated newer complement molecules such as pentraxin3 (PTX3)[16] and ficolins,[17,18] after stroke to determine some more sensitive and specific markers.

PTX3, one long pentraxin that conserves the c-terminal domain of the classical short pentraxins like CRP but differs because of having an unrelated long N-terminal domain, is one of the pattern-recognition receptors implicated in initial steps of complement cascade activation prior to CRP.[16] Release of PTX3 from macrophages, neutrophils, endothelial and smooth muscle cells appears to be in response to infectious or non-infectious inflammatory states like atherosclerosis.[19] Considering its interaction with atherosclerosis conditions such as acute myocardial infarction and unstable angina,PTX3 could have a superior prognostic value compared to CRP, Troponin-T (TnT), and ceratin kinase (CK).[19,20] Although one study showed such prognostic value after stroke,[16] but its association with stroke severity was unclear.

Lectin pathway, which is activated by MBL and ficolins, is the main complement pathway responsible after stroke.[18] There are three types of ficolins: M-ficolin (monocyte) or ficolin-1, L-ficolin (liver) or ficolin-2, and H-ficolin (Hakta antigen) or ficolin-3. Study of George Fust et al. demonstrated a negative correlation between ficolin-3 and stroke in such a way that low ficolin-3 levels were associated with unfavorable outcome after stroke.[18] We found no more studies evaluating the association of M-ficolin with stroke severity and its outcomes.

Pulmonary surfactants are lipoproteins synthesized by type II alveolar cells that reduce surface tension at alveolar-air interface. Four main surfactant proteins have been recognized: surfactant protein (SP) A, SPB, SPC, and SPD. SPA, which is the major component of surfactant proteins as well as a member of collectin family of C-type lectins, plays some roles in innate immunity of lungs via imitating C1q in activation of classical complement pathway. SPA is also found in some other tissues like prostate, spleen, mesothelium, gastrointestinal tract, and synovial;[21] but there is no available data in brain after stroke.

The purpose of this study was to determine the association of the serum levels of three complement molecules of PTX3, M-ficolin, and SPA, each related to one pathway, with the severity of ischemic stroke. Evaluating such association may suggest some new pharmacologic as well as prognostic markers of ischemic stroke.

MATERIALS AND METHODS

Our cross-sectional study was conducted on 89 adult patients older than 21 years suffering from ischemic stroke during 2014-2015 at emergency department of Shahid Beheshti Hospital of Kashan. The diagnosis was made according to clinical symptoms as well as signs and also brain computed tomography (CT) and magnetic resonance imaging (MRI) after 24-96 hours of emerging clinical symptoms. Patients with any acute infection or inflammatory state, acute myocardial infarction, and renal failure (GFR<30) were excluded. Three patients were excluded because of rheumatoid arthritis, hemorrhagic stroke, hemolysis of blood sample, and four patients due to sepsis after stroke. Finally, 82 patients completed the study. The ethical committee of the Kashan University of Medical Sciences approved the project and informed consent was obtained from each patient or patient's kin according to patient general condition.

Serum samples were obtained from all patients at 24-96 hours after emerging of stroke symptom and stored immediately at -80 centigrade until the assays were performed. Serum levels of PTX3, M-ficolin, and SPA were measured by Cusibo kit, (England), using a sandwich enzyme linked immunosorbent assay (ELISA) method according to manufacturer's protocol. CRP levels were measured by the agglutination method.

Patient's demographic data (age, sex) and traditional risk factors including hypertension, diabetes, hyperlipidemia, current smoking, history of previous stroke or transient ischemic attack (TIA), history of coronary vascular disease, and current consumption of aspirin or warfarin were obtained. The severity of stroke was scored on admission time according to modified National Institute of Health Stroke Scale (mNIHSS).[22]

The mNIHSS consists of 11 items and 31 total scores. Score of 1-5 was considered as minor, 6-14 as moderate, and 15-31 as severe stroke.[23]

The data were analyzed by SPSS17 SPSS Inc., Chicago, IL, USA).A *p*. value<0.05 was considered significant. Pearson's correlation test and Spearman's test were used according to data distribution to determine linear relationship between the variables. Independent t-test determined differences between the groups and ANOVA test was used to evaluate the association between the complement markers and stroke severity.

RESULTS

Baseline and clinical characteristics of study population are summarized in Table1.

The mean serum levels of PTX3, M-ficolin, and SPA in different severities of mild, moderate, and severe stroke are shown in Table 2. The more severe the stroke was, the higher levels of serum level of PTX3, M-ficolin, and SPA (p<0.001) were.

There was a significant correlation between PTX3, M-ficolin, and SPA with stroke severity according to mNIHSS score (p<0.001) (Table 3). The mean serum level of CRP increased in line with the stroke severity (p=0.022) which is lower than our three considered markers (Table 3). Such association of different markers remained significant even at the presence of confounding effects of age, diabetes, hypertension, hyperlipidemia, smoking, and stroke/TIA history in multivariate regression model (Table 4). Every unit increase in the level of mNIHSS increased the serum level of PTX3 as 0.47, M-ficolin as 0.08 and SPA as 4.9 units in regression model.

Table1. Demographic and clinical characteristics of patients with ischemic stroke

Variable	Description	N (%)	*P* - value
Age	(Mean±SD)	70.2±14.3	-
Sex	Male	42 (51.2%)	0.55
	female	40 (48.8%)	
Diabetes mellitus	Yes	25 (30.5%)	0.566
	No	57 (69.5%)	
Hypertension	Yes	51 (62.2%)	0.176
	No	31 (37.8%)	
Hyperlipidemia	Yes	24 (29.3%)	0.52
	No	58 (70.7%)	
Stroke/TIA history	Yes	17 (20.7%)	0.32
	No	65 (79.3%)	
CVD History	Yes	22 (26.8%)	0.133
	No	60 (73.2%)	
Anticoagulant	ASA	25 (30.5%)	0.958
	Warfarin	6 (7.3%)	
	Non	51 (62.2%)	
Smoker	Yes	13 (15.9%)	0.542
	Previous	2 (2.4%)	
	No	67 (81.7%)	
mNIHSS	Mean±SD	8.26±5.58	-
PTX3	Mean±SD	7.15±3.66	-
M-ficolin	Mean±SD	1.49±0.61	-
SPA	Mean±SD	88.29±37.13	-
CRP	Mean±SD	15.52±19.25	-
Stroke severity	Mild	37 (45.1%)	
	Moderate	27 (32.9%)	-
	Severe	18 (22.0%)	

SD, standard deviation; TIA ,transient ischemic attack; CVD, coronary vascular disease; mNIHSS , modified national institute of health stroke scale; PTX3, pentraxin 3; M-ficolin, monocyte ficolin; SPA, surfactant protein A; CRP ,C-reactive protein; ASA, acetyl salicylic acid;

Table 2. Mean serum level of PTX3, M-ficolin, SPA, and CRP in different stroke severities (mNIHSS)

Stroke severity / Molecules	Mild (Mean±SD)	Moderate (Mean±SD)	Severe (Mean±SD)	*p*[*]
PTX3 (pg/ml)	4.53±1.42	8.18±3.18	10.98±3.47	<0.001
M-ficolin (pg/ml)	1.06±0.31	1.60±0.48	2.21±0.52	<0.001
SPA (pg/ml)	67.98±16.36	85.47±29.19	134.27±42.49	<0.001
CRP (mg/l)	10.38±11.16	18.74±19.68	21.23±28.31	0.047

[*]ANOVA test; PTX3, pentraxin 3; M-ficolin, monocyte ficolin; SPA, surfactant protein A; CRP, C-reactive protein; mNIHSS, modified national institute of health stroke scale

Table 3. Correlation of PTX3, M-ficolin, SPA, and CRP with stroke severity (Pearson's correlation test)

Variable	Correlation	Sig.
PTX3[*]	0.723	<0.001
M-ficolin[**]	0.736	<0.001
SPA[***]	0.731	<0.001
CRP[****]	0.253	0.022

[*]dependent variable: PTX3 [**]dependent variable: M-ficolin [***]dependent variable: SPA [****]dependent variable: CRP
PTX3, pentraxin 3; M-ficolin, monocyte ficolin; SPA, surfactant protein A; CRP ,C-reactive protein;

Table 4. Association of serum levels of PTX, M-ficolin, SPA and CRP with mNIHSS in separate multivariate models

Outcome	Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
PTX3[*]	(Constant)	2.425	1.640		1.479	0.144
	mNIHSS	0.470	0.057	0.716	8.254	0.000
	Age	0.016	0.021	0.064	0.762	0.449
	Sex	-0.865	0.748	-0.119	-1.157	0.251
	Stroke history	-0.159	0.739	-0.018	-0.215	0.830
	DM	0.379	0.684	0.048	0.555	0.580
	HTN	-0.201	0.685	-0.027	-0.293	0.770
	Hyperlipidemia	-0.507	0.735	-0.063	-0.690	0.493
	Smoking	1.604	0.720	0.203	2.228	0.029
M-ficolin[**]	(Constant)	0.683	0.269		2.541	0.013
	mNIHSS	0.079	0.009	0.725	8.514	0.000
	Age	0.002	0.004	0.041	0.501	0.618
	Sex	0.060	0.123	0.050	0.491	0.625
	Stroke history	-0.071	0.121	-0.047	-0.587	0.559
	DM	-0.087	0.112	-0.066	-0.780	0.438
	HTN	0.054	0.112	0.043	0.478	0.634
	Hyperlipidemia	0.144	0.121	0.107	1.191	0.238
	Smoking	-0.179	0.118	-0.136	-1.514	0.134
SPA[***]	(Constant)	58.240	16.609		3.507	0.001
	mNIHSS	4.873	0.577	0.733	8.451	0.000
	Age	-0.092	0.217	-0.036	-0.424	0.673
	Sex	-11.452	7.577	-0.155	-1.511	0.135
	Stroke history	2.445	7.482	0.027	0.327	0.745
	DM	-0.891	6.924	-0.011	-0.129	0.898
	HTN	1.466	6.942	0.019	0.211	0.833
	Hyperlipidemia	-2.356	7.444	-0.029	-0.316	0.753
	Smoking	8.083	7.291	0.101	1.109	0.271

[*]dependent variable: PTX3 [**]dependent variable: M-ficolin [***]dependent variable: SPA PTX3, pentraxin 3; M-ficolin, monocyte ficolin; SPA, surfactant protein A; CRP ,C-reactive protein; mNIHSS, modified national institute of health stroke scale; DM, diabetes mellitus; HTN, hypertension;

DISCUSSION

Complement system, one of the most important components of immune system, contributes also in stroke pathogenesis.[2,3] It seems that inhibition of complement system could reduce the size of infarcted area as well as neurologic damage.[2,6] Our study demonstrated, to best of our knowledge for the first time, a strong correlation between 3 molecules of PTX3, M-ficolin, and SPA with stroke severity score. Such correlation was stronger than that of well-known inflammatory molecule CRP and remained significant even after adjusting the effect of confounders. This concept may introduce those complement activators as clinically valuable markers to determine stroke severity in acute phases. It is likely that in more severe types of stroke, more de novo or induced production of such markers, as a manifestation of their inflammatory function, constitutes a circulatory reservoir that supplies their CNS-consumed quantities.[24,25]

In line with our study, Wi-sun Ryu et al. showed higher levels of PTX3 which was independently associated with increased mortality after ischemic stroke. They also introduced PTX3 as a more predictive marker of mortality than age, CRP, and mNIHSS as stroke severity score. The combination of PTX3 and NIHSS had higher discriminatory accuracy than PTX3 and NIHSS alone.[16] Similar to stroke events, the relationship of PTX3 activation with atherosclerosis progression has mostly been studied in coronary vascular diseases.[16,19,26-28] Some studies suggest that deficiency of PTX3 is associated with increased cardiac damage and mortality. Therefore, PTX3 may potentially play some cardiovascular protective roles.[28,29] According to this idea, increased serum levels of PTX3 in our study may be a compensatory mechanism to overcome the severity of stroke through its neurogenic as well as angiogenic effects which improves motor function.[30] Paradoxically, others believe that PTX3 has some pro-inflammatory effects which lead to damaging consequences of inflammation and in this regard it is associated with poor outcomes. So anti-infalmmatory or proinflammatory role of PTX3 is challenging .[16,19,26,27] Latter idea supports increased amounts of PTX3 in our study as a pathologic marker causing more severe forms of stroke.

In consistence with other studies,[12,18,31] our study supports the role of lectin pathway in the pathogenesis of stroke. However, changes in serum level of ficolins after stroke seem to be different, regarding the severity as well as outcomes of stroke. For example George Fust et al. showed a decreased concentration of both H and L-ficolin in admission time as well as early follow-up of patients with ischemic stroke compared to healthy subjects,[18] and R. Zangari et al found a decreased (at 6 hours) and then, in agreement with our study (in the case of M-ficolin), increased (at 48 hours) concentration of both M and L-ficolins and consistent decreased levels of H-ficolin at both times after the ischemic stroke.[25] George Fust et al found an inverse correlation between H-ficolin concentration and stroke severity according to mNIHSS stroke scale, infarction size, and worsen outcome, and

R. Zangari et al revealed a selective inverse relationship between L-ficolin concentrations at 6-hours after the stroke and 3-month unfavorable outcomes. The reverse relationship between H and L-ficolins and stroke severity could be due to their local consumption in acute stroke. However, we showed a positive correlation between the serum levels of M-ficolin measured 24-96 hours after the stroke with stroke severity. Like previous findings,[3,13,32,33] this study also revealed a higher association of CRP level with poor outcomes.

Current study demonstrated that serum level of SPA goes up with increasing stroke severity. Previous studies have shown activation of SPA, one of the complement activators, in (the inflammation of) some tissues like alveolus, prostate, spleen, and mesothelium.[21] It seems that more studies are required to evaluate SPA activity after stroke.

The limitation of our study was that the serum concentrations were measured once in acute phase and there were no longitudinal follow-up samples to evaluate their changes during the time. This limitation allowed just a cross-sectional analysis with only a limited robustness.

Our three studied complement molecules showed a strong correlation with stroke severity. Such correlation was even more than CRP. These findings may be used for both diagnostic approaches of stroke severity and therapeutic strategies.

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