ORIGINAL ARTICLE

Serum CRP Concentrations and Severity of Ischemic Stroke Subtypes

Yun Luo, Zhongyuan Wang, Jingwei Li, Yun Xu

ABSTRACT: ***Objective:*** The aim of this retrospective study was to investigate if elevated C reactive protein (CRP) was related to the stroke severity, and to analyze its different distribution in stroke subtypes. ***Methods:*** 316 patients with acute ischemic stroke (AIS) were enrolled and had CRP determinations; they were dichotomized as<7 or≥7mg/L according to the previous report. 128 patients with transient ischemic attack who also had CRP measurements were selected as controls. A possible level-risk relationship between elevated CRP and NIHSS, which considered relatively severe illness as a value≥8, was studied within the AIS group. ***Results:*** CRP was elevated in 21% of the AIS compared to 4% in the control group (p = 0.000). Within the AIS group, patients with CRP levels ≥7mg/L had a significantly increased risk of severe stroke (OR 3.33, 95% CI 1.84-6.00, p =0.00). In subtype stroke, the highest rate of elevated CRP and NIHSS were in those with cardioembolic stroke (CE) using TOAST classification, total anterior circulation infarction (TACI) of OCSP classification and large volume infarction (LVI) of Adams classification; the odds ratio(OR) between elevated CRP and NIHSS was 6.14 (95% CI 1.43-26.44) in CE, 1.714 (95% CI 1.30-2.26) in TACI, 2.32 (95% CI 1.08-4.99) in LVI, and the p value were all below 0.05. ***Conclusion:*** Elevated CRP level can reflect the severity of AIS, which was association with stroke subtype.

RÉSUMÉ: Concentration sérique de CRP et sévérité des sous-types d'accidents vasculaires cérébraux. ***Objectif :*** Le but de cette étude rétrospective était d'examiner si un taux élevé de protéine C réactive (CRP) était relié à la sévérité de l'accident vasculaire cérébral (AVC) et d'analyser sa distribution selon les sous-types d'AVC. ***Méthode :*** Trois cent seize patients atteints d'un AVC ischémique aigu (AVCIA) et dont le taux de CRP avait été déterminé ont été étudiés. Nous avons séparé les patients en deux groupes selon que leur taux de CRP était < 7 mg/L ou ≥ 7 mg/L. Cent vingt-huit patients atteints d'ischémie cérébrale transitoire (ICT) dont le taux de CRP avait également été déterminé antérieurement ont été choisis comme témoins. Nous avons examiné s'il existait une relation entre le niveau de CRP et le score au NIHSS, une valeur ≥ 8 étant considérée comme témoignant d'une maladie relativement sévère, dans le groupe atteint d'un AVCIA. ***Résultats :*** Le taux de CRP était élevé chez 21% des patients du groupe AVCIA contre 4% chez le groupe témoin (p = 0,000). Dans le groupe AVCIA, les patients dont le taux de CRP était ≥ 7 mg/L avaient un risque significativement plus élevé que leur AVC soit sévère (RC 3,33 ; IC à 95% 1,84 à 6,00 ; p = 0,00). Selon les sous-types d'AVC, le taux le plus élevé de CRP et le score le plus élevé au NIHSS étaient chez ceux qui avaient subi un AVC cardioembolique (CE) selon la classification TOAST, un infarctus complet de la circulation antérieure (ICCA) selon la classification OCSP et un infarctus très étendu (IE) selon la classification d'Adams (RC entre un taux élevé de CRP et NIHSS 6,14 ; IC à 95% 1,43 à 26,44 pour l'AVC CE ; RC 1,714 ; IC à 95% 1,30 à 2,26 pour l'ITCA ; RC 2,32 ; IC à 95% 1,08 à 4,99 pour un IE) et les valeurs de p étaient toutes < 0,05. ***Conclusion :*** Un taux élevé de CRP peut refléter la sévérité d'un AVCIA et la sévérité de l'AVC était associée au sous-type d'AVC.

Can. J. Neurol. Sci. 2012; 39: 69-73

Elevated serum C reactive protein (CRP) concentrations have been found in acute ischemic stroke (AIS) patients[1-10], which reflects a systemic inflammatory response following stroke[1]. It is possible that the increased CRP has a close relationship with the extent of cerebral tissue injury[2]. Previously studies paid more attention to its prognostic role of outcome, however, study on the correlation between elevated CRP levels and stroke severity, especially with the stroke subtype is limited.

The aim of this retrospective study was to investigate elevated CRP in relation to stroke severity, and analyze its different distribution in stroke subtypes. Here, three subtypes of ischemic stroke were studied, taking into account etiology and clinical and image classification.

Methods

Study design

Data for this study were obtained at Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, and were collected from all AIS patients admitted to the department of neurology from October 2008 to January 2011. Patients who were found with pre-stroke impairment or infections or inflammatory diseases were excluded. Also, patients who were admitted more than ten days after the onset of symptoms were excluded. At admission, plain computed tomogram (CT) scan of the head was done to rule out haemorrhage and magnetic resonance imaging (MRI) was done to identify the new infarction, otherwise such patients would be

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Received July 12, 2011. Final Revisions Submitted August 23, 2011.

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excluded. Simultaneously, 128 patients with transient ischemic attacks (TIAs), who were age- and sex-comparable subjects, were selected in the same time period as the control group. Blood samples for CRP were drawn on admission, and analyzed within 24 hour by a solid-phase chemiluminescent immunometric assay on Immulite 2000 with the manufacturer's reagents as directed.

Baseline variables

Baseline clinical information was obtained for all patients, including time of the symptom onset to admission, stroke subtype, stroke severity assessed with the National Institutes of Health Stroke Scale (NIHSS) by two neurologists at admission, and cardiovascular risk factors were noted. Age was categorized as <50, 50–59, 60–69, 70-79 and ≥80 years. The level of CRP was categorized as <7mg/L and ≥7mg/L (Due to the skewed distribution of CRP, we chose a somewhat arbitrary cut off point for CRP: values below 7mg/L were considered normal)[11]. National Institutes of Health Stroke Scale values were dichotomized at 8, which was considered as relatively severe illness[12].

Stroke subtype

TOAST was chosen for the primary etiological subtype analyses, which included large-vessel disease (LVD), small-vessel disease (SVD), cardioembolic (CE), cryptogenic stroke, and other strokes. In our study, the last two types were combined to others. Oxford Community Stroke Project (OCSP) is a clinical classification used in population studies, which provides information on the clinical extent of brain damage, including total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), lacunar infarction (LACI), posterior circulation infarction (POCI). According to the Adams criteria, images can be divided into lacunar infarction (LACI), small volume infarction (SVI) and large volume infarction (LVI).

Statistical analysis

Statistical analyses were performed with SPSS 13.0 for Windows. The results are expressed as percentages for categorical variables (Pearson $\chi 2$ test) and as mean ±SEM for the continuous variables(t-test) depending on their normal distribution. Level of significance for statistical purposes was $p<0.05$. The relation between dichotomized CRP and NIHSS was expressed as an odds ratio (OR), with a corresponding 95% confidence interval (CI), through logistic regression.

Results

Table 1 shows the prevalence of an elevated CRP of AIS according to various potential predictors, such as age and sex, pre-existing illnesses, such as diabetes mellitus and hypertension, stroke severity, such as NIHSS and time to hospital. Three hundred and sixteen patients were included in the

Table 1: Prevalence of an elevated CRP in various patient subgroups

		Prevalence of elevated CRP (>=7 mg/L)	
Group		%	Univariate p-value
Age	<50	11(3/27)	0.273
	50-59	22(14/63)	
	60-69	18(12/67)	
	70-79	27(30/111)	
	80+	17(8/48)	
Sex	Male	21(41/199)	0.734
	Female	22(26/117)	
Time to hospital	(0, 24 hours)	21(25/121)	0.197
	[24hours, 3days)	27(30/111)	
	[3days, 7days)	14(7/49)	
	[7days, 10days)	14(5/35)	
Pre-existing diabetes mellitus	No	20(48/239)	0.391
	Yes	25(19/77)	
Pre-existing Hypertension	No	20 (19/95)	0.732
	Yes	22 (48/221)	
NIHSS	<8	16(40/247)	0.000
	≥8	39(27/69)	

https://doi.org/10.1017/S0317167100012713 Published online by Cambridge University Press

trial, among them, 199 were male and 117 were female, with age ranging from 15 to 91 years and time to hospital ranging from 2 hours to 10 days[13]. There were 221 patients with hypertension and 77 patients with diabetes mellitus coexisting with AIS, but whose distribution was similar to the control group (data not shown), and 69 patients had severe stroke with NIHSS≥8. In univariate analysis, NIHSS ≥8 and NIHSS <8 showed a significant difference for elevated CRP (p=0.000).

As shown in the Figure, 21% elevated CRP was found in the AIS compared to 4% in the control group (p = 0.000); AIS patients with NIHSS levels ≥8 more often had a elevated CRP than patients with lower NIHSS levels (39 versus 16%; p = 0.000). Patients with CRP levels ≥7 mg/L more often had a severe illness (40 versus 17%; p = 0.000) or high NIHSS level (7.6±0.85 versus 4.3±0.27; p = 0.000) than patients with lower CRP level. A level-risk relationship was observed between elevated CRP and elevated NIHSS: the OR was 3.327 (95% CI 1.844-6.003); p value was 0.000 (Table 3).

Among the three stroke subtypes, there were significant difference in elevated CRP and NIHSS. In the TOAST classification, elevated CRP and NIHSS percent were highest in CE stroke and lowest in SVD stroke, and both of them were highest in LVI and lowest in LACI using the Adams classification. Also, the same trend was observed in the OCSP subtype, with the highest rate of elevated CRP and NIHSS in the TACI and lowest in the LACI groups (Table 2). The level-risk relationships between elevated CRP and elevated NIHSS in stroke subtypes were investigated: the OR was 6.139(95% CI 1.43-26.438) in CE, 1.714(95% CI 1.301-2.259) in TACI, 2.323(95% CI 1.081-4.991) in LVI, and the p value were all below 0.05 (Table 3).

Discussion

Studies have shown that increased CRP levels are associated with more severe short-term and long-term prognosis in patients with AIS[6,9,10,14-17]. C reactive protein values are higher in AIS patients at admission, and are correlated with stroke severity[18]. C reactive protein is a marker of the local severity of "brain attack"[19,20]. This study showed that the rate of elevated CRP was higher in the AIS than in the control group; higher CRP was more prevalent in the severe stroke in terms of NIHSS score, and similarly, a higher incidence of severe stroke was more prevalent in the elevated CRP group. All our findings revealed that elevated CRP reflects the severity of ischemic stroke in the acute phase, which is consistent with previous reports.

Few studies have investigated the relationship between CRP and stroke subtypes[6,8,9,13,18]. Oxford Community Stroke Project

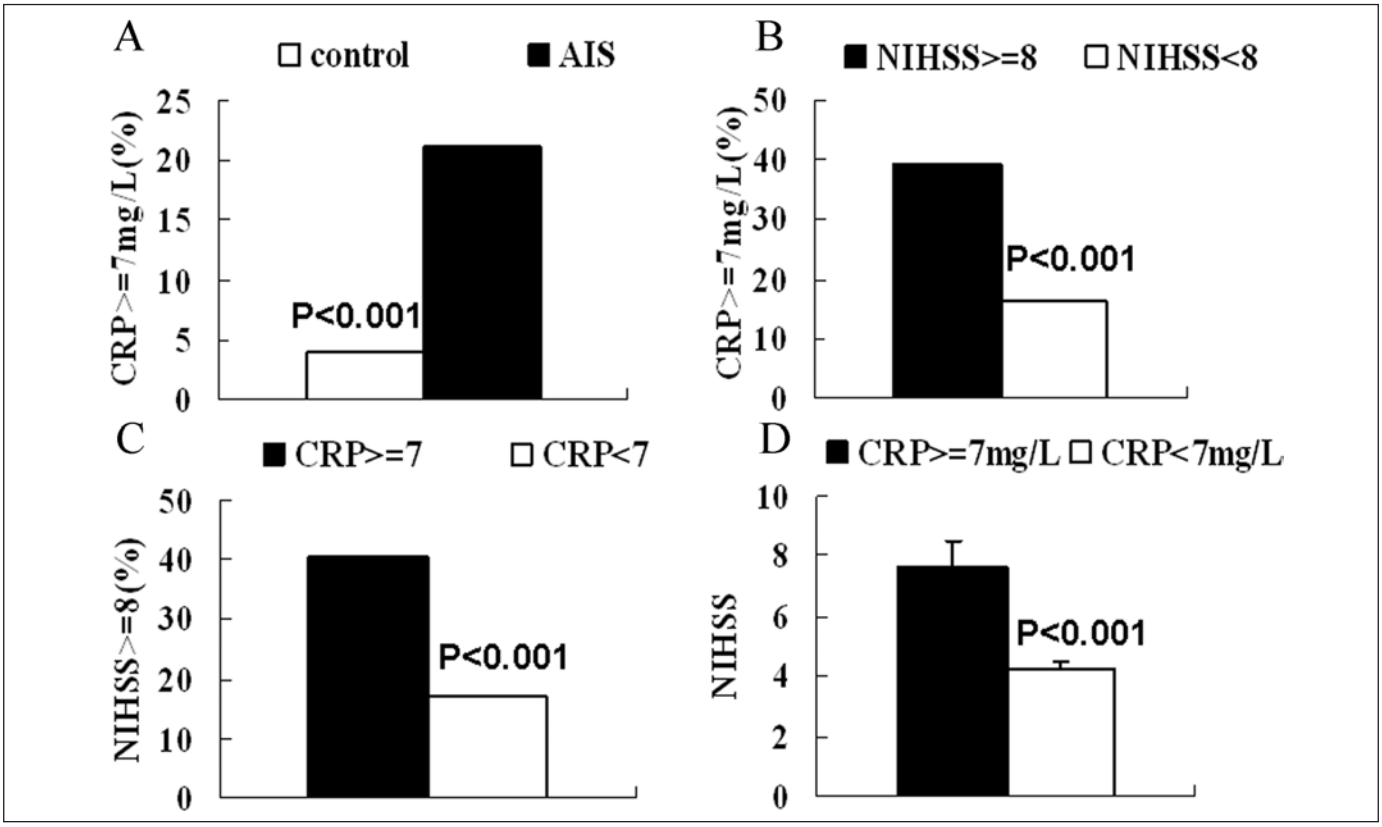

Figure: *Association of CRP levels on admission with the severity of AIS. A-The percent of CRP≥=7 in the AIS and control group; B- The percent of CRP≥=7 in the NIHSS≥=8 and <8 control group of AIS; C- The percent of NIHSS≥=8 in the CRP≥=7 and <7 group of AIS; D-comparison of NIHSS between CRP≥=7 and <7 group.*

https://doi.org/10.1017/S0317167100012713 Published online by Cambridge University Press

Table 2: Prevalence of an elevated CRP and NIHSS in Stroke Subtype

Stroke subtype		CRP≥7(%)	NIHSS≥8 (%)
TOAST	LVD	21(30/140)	21(30/140)
	CE	36(16/45)	56(25/45)
	SVD	13(9/68)	1(1/68)
	Others	19(12/63)	21(13/63)
p-value		0.04	0.000
OCSP	TACI	34(15/44)	82(36/44)
	PACI	19(29/152)	19(29/152)
	POCI	28(11/39)	8(3/39)
	LACI	15(12/81)	1 (1/81)
p-value		0.048	0.000
Adams	LACI	12(4/34)	3(1/34)
	SVI	14(22/159)	8(13/159)
	LVI	33(41/123)	45(55/123)
p-value		0.000	0.000

is a clinical classification and the Adams is an image classification; both provided information about the extent of lesion. To our knowledge, no studies on CRP in the Adams subtype (only one examined the OCSP subtype) showed that elevated CRP was associated with increased stroke severity or that the most common stroke subtype in the high CRP group was TACI[18]. Our study demonstrated that elevated CRP showed different distribution in OCSP and Adams subtypes, accordingly the most common subtype is TACI and LVI, with the most severe stroke. A positive association between elevated CRP and NIHSS is exclusive compared to the others. Relatively, there were more studies referring to TOAST subtypes[8,13,18]. In line with our results, cardioembolic etiology tends to cause elevated CRP with higher stroke severity. Elevated CRP can reflect the severity of ischemic stroke; in addition, stroke subtype is an important factor in relation to this trend.

Increased CRP is related to infarct size in acute stroke[21,22]. Our intra-subtype analysis showed the highest proportion of elevated CRP was found in TACI and LVI, suggesting that a more intense inflammatory response is related to infarct size. With regard to etiological subtype, the highest proportion of elevated CRP was observed in CE stroke, which was most

Table 3: Association between elevated CRP (≥7mg/L) and elevated NIHSS (≥8) in ischemic stroke and its Subtype

Stroke subtype		OR	95% CI	P
TOAST	LVD	2.25	0.914-5.537	0.073
	CE	6.139	1.43-26.438	0.013
	SVD	0.983	0.951-1.017	0.148
	Others	2.333	0.576-9.458	0.249
OCSP	TACI	1.714	1.301-2.259	0.037
	PACI	2.318	0.923-5.821	0.069
	POCI	1.091	0.920-1.294	0.148
	LACI	6.000	0.485-74.29	0.187
Adams	LACI	0.967	0.905-1.033	1.000
	SVI	1.145	0.236-5.554	1.000
	LVI	2.323	1.081-4.991	0.029
TOTAL		3.327	1.844-6.003	0.000

https://doi.org/10.1017/S0317167100012713 Published online by Cambridge University Press

prevalent in the TACI and LVI group[13]. Also, the severity of the neurological deficit after AIS is correlated with infarct volume[23]. In our study, TACI, LVI and CE subtypes exhibited more severe stroke, which was in accordance with previous reports.

In summary, our current study provides evidence that elevated CRP can reflect the severity of AIS, and may be used as a marker to monitor the state of illness, especially in the CE, TACI and LVI subtypes of stroke. Due to ease of measurement, this method can be widely used.

Acknowledgments

This work was supported by the National Nature Science Foundation of China (30971010, 30670739, 81000510), outstanding Researcher Program (RC2007006) and the National Nature Science Foundation (BK2009037) of Jiangsu Province of China, and funding from the State Key Laboratory of Pharmaceutical Biotechnology of Nanjing University (KF-GN-200901), and the 973 Program from the Ministry of Science and Technology of China (2009CB521906), and the Fundamental Research Funds for the Central Universities (021414340051).

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