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High-sensitivity C-reactive protein as an indicator of ischemic stroke in patients with isolated acute vestibular syndrome

Retrospective observational study

Fangju Lin, MD, Ying Chen, MM, Min Wan, MD, Wei Chen, MM, Weihua Jia, MD*

Abstract

Ischemic strokes presenting with isolated acute vestibular syndrome (AVS) are not rare and still are challenging for diagnosis. In this retrospective study, we aimed to investigate the association of high-sensitivity C-reactive protein (hs-CRP) with stroke in patients with isolated AVS. A total of 217 patients with isolated AVS within 3 days of symptom onset were included. Serum hs-CRP levels were assessed within 24 hours of admission. The relationship between hs-CRP levels and stroke in patients with AVS were analyzed using univariate and multivariate models. The results showed that hs-CRP levels were significantly higher in infarction patients than that in noninfarction group. The stroke occurrence was increased with increasing quartile levels of hs-CRP. The highest quartile level of hs-CRP was associated with a higher occurrence of stroke compared with the lowest quartile group (adjusted odds ratio [OR], 4.099; 95% confidence interval [CI], 1.272–13.216; $P = .018$). We also found that male gender (adjusted OR, 5.635; 95% CI, 2.212–14.352; $P < .001$) and increased low-density lipoprotein cholesterol (LDL-C) (adjusted OR, 2.543; 95% CI, 1.175–5.505; $P = .018$) were independently associated with stroke in patients with AVS. In addition, using the receiver operating characteristic curve analysis, our study yielded a threshold value of hs-CRP at 1.82 mg/L, and demonstrated that combining hs-CRP with LDL-C improved the discriminatory ability to identify stroke patients with AVS (area under the curve of the combined model: 0.753; 95% CI = 0.684–0.821; $P < .001$). Hs-CRP may be a useful indicator of stroke in patients with AVS. More attention should be paid to the patients with elevated hs-CRP level.

Abbreviations: AVS = acute vestibular syndrome, BPPV = benign paroxysmal positional vertigo, CE = cardioembolism, CI = confidence interval, CT = computerized tomography, DWI = diffusion-weighted imaging, ESR = erythrocyte sedimentation rate, HbA1c = glycated hemoglobin A1c, HINTS = head impulse test-nystagmus pattern-test of skew, Hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile ranges, LAA = large-artery atherosclerosis, LDL-C = low-density lipoprotein cholesterol, MRI = magnetic resonance imaging, OR = odds ratio, ROC = receiver operating characteristic, SAO = small artery occlusion, SD = standard deviation, SOE = stroke of other determined etiology, SUE = stroke of undetermined etiology, TOAST = Trial of ORG10172 in Acute Stroke Treatment.

Keywords: acute vestibular syndrome, high-sensitivity C-reactive protein, low-density lipoprotein cholesterol, posterior circulation stroke

1. Introduction

Acute dizziness or vertigo, accompanied or not by nausea or vomiting, and gait unsteadiness, is characteristic of acute vestibular syndrome (AVS).[1] The origins of AVS are briefly ascribed to 2 parts, the peripheral and central disorders involving the vestibule, cerebellum, and their connective nerve fibers.[2] AVS with focal neurologic deficits are strongly indicative of posterior circulation stroke.[3] However, it may be challenging for diagnosis when isolated AVS present as onset symptoms of stroke. It has been reported that approximately 25%, more often than previously believed, of the posterior circulation stroke patients present with isolated AVS.[4] Furthermore, early magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) are occasionally false-negative in those stroke patients with AVS.[5] The short time interval from the symptom onset to MRI scans and relatively small lesions might explain the false-negative results.[6] Another useful tool to identify stroke patients with AVS is HINTS (head impulse test, nystagmus pattern, and test of skew), a bedside examination which has been proved to be more sensitive than MRI scan for the diagnosis of stroke with AVS.[7] However, not all examiners are qualified for the HINTS evaluation, and some patients with transient vertigo have recovered from nystagmus before HINTS examination or some other patients with severe and persistent vertigo usually cannot complete the examination.[8] Therefore, the limitations of neuroimaging and HINTS assessment highlight the importance

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of seeking a readily available biomarker to enhance early recognition and diagnosis of stroke in patients with AVS.

Inflammation is widely recognized to play a crucial role in initiation and progression of atherosclerosis. High-sensitivity C-reactive protein (hs-CRP) has emerged as one of the important inflammatory markers associated with cerebrovascular disease.[9] Previous large studies have indicated that elevated CRP was associated with increased risk of first-ever ischemic stroke[10] and recurrence of stroke.[11] Furthermore, hs-CRP is predictive of functional outcome and future mortality in stroke patients.[12] However, the association of hs-CRP with the stroke in patients with isolated AVS has not been studied. Thus, we would aim to explore the hs-CRP level in patients with AVS and analyze the relationship between hs-CRP and ischemic stroke in such special patient population, in an attempt to provide a useful indicator for early recognition and diagnosis.

2. Methods

2.1. Subjects

We retrospectively selected patients with isolated AVS hospitalized in the neurology department of Shijingshan Hospital from September 2016 to January 2018. The study was approved by the Ethics Committee of Shijingshan Hospital and the written informed consent was obtained from the patients or their legal proxies. The inclusion criteria were as follows: age ≥18 years; acute onset of vestibular syndrome (admitted within 3 days after symptom onset); lack other symptoms or signs of focal neurological impairment. The exclusion criteria were as follows: vertigo caused by benign paroxysmal positional vertigo (BPPV), aural or ophthalmic disease, medication/drug intoxication, psychological disorder, or systemic diseases such as infection, hypoglycemia, and cardiac insufficiency.

2.2. Research methods

The following demographic and clinical data were collected: age, gender, past medical history, smoking or drinking status, serum hs-CRP, and other common laboratory index. Fasting blood samples were collected from each patient within 24 hours of admission. Level of hs-CRP was assessed using an immunoturbidimetric assay in the certified clinical laboratory in Shijingshan hospital.

A cerebral computerized tomography (CT) scan was conducted for each patient within an hour of admission to the hospital. Patients underwent a cerebral MRI (including T1 weighted image, T2 weighted image, DWI, and fluid attenuated inversion recovery sequence) within 48 hours of hospitalization, and patients with the contraindication to MRI received a repeat cerebral CT examination. The presence of acute ischemic stroke was confirmed by high DWI signal and low apparent diffusion coefficient signal combined with other MRI sequences or low density on CT scan according to World Health Organization criteria. Patients were divided into infarction group and noninfarction group. Strokes were etiologically categorized according to the Trial of ORG10172 in Acute Stroke Treatment (TOAST) classification.

2.3. Statistical analysis

Data were expressed as number (n) and percentage for categorical variables, and median (interquartile ranges) for continuous variables. The Chi-squared and the Mann–Whitney *U* test were performed for categorical and continuous variables respectively to compare the 2 groups. Multivariate logistic regression model was used to analyze the association of hs-CRP with stroke in patients with AVS, after adjustment for the possible confounders and variables with $P < .10$ in the univariate analysis. Receiver operating characteristic (ROC) curves analysis was used to test the discriminatory ability of the hs-CRP. $P < .05$ was considered statistically significant. Statistical analysis was conducted with SPSS 24.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient demographics and baseline characteristics

Of 243 patients with AVS hospitalized during the study period, a total of 217 patients were included in the final analysis, after excluding patients with BPPV (12 patients), psychological disorder (3 patients), infection (5 patients), and hypertension (6 patients). There were 56 patients diagnosed with cerebral infarction, with a mean age of 68.8 ± 11.0 years old (range, 49–85 years old), of which 45 patients were men, a higher percentage compared with the noninfarction group (80.4% vs 47.8%, $P < .001$). Moreover, the infarction cases had higher prevalence of hypertension history (62.5% vs 47.2%, $P = .049$) and higher level of hs-CRP compared with the noninfarction group (2.71 [1.32–4.09] vs 1.26 [0.64–2.46] mg/L, $P < .001$). The levels of leukocyte, neutrophil, low-density lipoprotein cholesterol (LDL-C), and HbA1C were also significantly higher in stroke patients than those without stroke ($P < .05$). There was no statistically significant difference between the 2 groups regarding other baseline characteristics. According to the TOAST classification, small artery occlusion (SAO) subtype accounted for a substantial part in infarction group (Table 1).

3.2. Demographics and characteristics of patients according to hs-CRP quartiles

Hs-CRP values were divided into 4 levels by quartiles as follows: quartile 1 (Q1), <0.73 mg/L; quartile 2 (Q2), 0.73 to 1.50 mg/L; quartile 3 (Q3), 1.50 to 3.06 mg/L; and quartile 4 (Q4), >3.06 mg/L. Occurrence of stroke increased with increasing hs-CRP quartiles ($P < .001$). Besides this, histories of diabetes mellitus, levels of erythrocyte sedimentation rate (ESR), LDL-C, and HbA1C were significantly higher in patients with higher hs-CRP levels, compared with those with lower hs-CRP levels. Level of neutrophil tended to increase with higher hs-CRP levels, except for levels within the quartile 4. History of hyperlipemia and prior stroke and level of leukocyte were unequally distributed among the hs-CRP quartiles. There were no statistically significant differences among the quartiles regarding other characteristics (Table 2).

3.3. Univariate and multivariate logistic regression analysis of hs-CRP and other factors for stroke

The univariate analysis showed that the third and fourth quartile of hs-CRP was significantly associated with stroke in patients with AVS ($P < .05$), and multivariate logistic regression analysis indicated that the fourth quartile of hs-CRP remained markedly associated with stroke (adjusted odds ratio [OR], 4.099; 95% confidence interval [CI], 1.272–13.216; $P = .018$), independent of gender, age, and confounding factors with a *P* value <.10 in the univariate analysis. We found that male gender (adjusted OR = 5.635; 95% CI, 2.212–14.352; $P < .001$) and higher level of LDL-C (>2.6 mmol/L) (adjusted OR = 2.543; 95% CI, 1.175–

Table 1

Patient demographics and characteristics between infarction and noninfarction groups.

Characteristics	Cerebral infarction (n = 56)	Noncerebral infarction (n = 161)	P
Male, no. (%)	45 (80.4)	77 (47.8)	<.001
Age (years), mean ± SD	68.8 ± 11.0	71.4 ± 9.2	.083
Medical history, no. (%)			
Hyperlipemia	36 (64.3)	86 (53.4)	.158
Hypertension	35 (62.5)	76 (47.2)	.049
Diabetes mellitus	31 (55.4)	66 (41.0)	.063
Coronary heart disease	19 (33.9)	40 (24.8)	.188
Atrial fibrillation	9 (16.1)	16 (9.9)	.216
Prior stroke	10 (17.9)	20 (12.4)	.310
Smoking history, no. (%)	30 (53.6)	60 (39.8)	.072
Drinking history, no. (%)	18 (32.1)	35 (21.7)	.119
Laboratory findings, median (IQR)			
Hs-CRP (mg/L)	2.71 (1.32–4.09)	1.26 (0.64–2.46)	<.001
Leukocyte ($\times 10^9$/L)	8.7 (7.1–9.7)	6.8 (5.7–8.6)	<.001
Neutrophil (%)	78.9 (66.9–85.1)	68.3 (58.8–77.0)	<.001
ESR (mm/h)	16.0 (8.3–22.0)	12.0 (6.0–19.5)	.065
LDL-C (mmol/L)	3.01 (2.42–3.48)	2.21 (1.77–3.03)	<.001
HbA1C (%)	6.7 (6.1–7.9)	6.2 (5.7–7.3)	.005
TOAST classification, no. (%)			
LAA	14 (25.0)		
CE	3 (5.4%)		
SAO	33 (58.9%)		
SOE	0		
SUE	6 (10.7%)		

CE = cardioembolism, ESR = erythrocyte sedimentation rate, HbA1c = glycated hemoglobin A1c, Hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile ranges, LAA = large-artery atherosclerosis, LDL-C = low-density lipoprotein cholesterol, SAO = small artery occlusion, SD = standard deviation, SOE = stroke of other determined etiology, SUE = stroke of undetermined etiology, TOAST = Trial of ORG10172 in Acute Stroke Treatment.

5.505; $P = .018$) were also significantly influential factors for stroke (Table 3).

3.4. ROC curve analysis for hs-CRP and LDL-C cutoff values

The ROC curve demonstrated that hs-CRP with a threshold value at 1.82 mg/L has a great discriminatory ability for stroke diagnosis in patients with AVS, and the area under the curve (AUC) was 0.699 (95% CI: 0.619–0.779, $P < .001$), similar to LDL-C (AUC 0.708; 95% CI 0.632–0.783, $P < .001$). Combining hs-CRP with LDL-C improved the diagnostic power (AUC of the combined model: 0.753; 95% CI = 0.684–0.821; $P < .001$) (Fig. 1).

4. Discussion

To our knowledge, the present study is the first to report the significant association of hs-CRP with ischemic stroke in patients

Table 2

Demographics and characteristics of patients according to high-sensitivity C-reactive protein quartiles.

	Q1	Q2	Q3	Q4	P
Male, no. (%)	31 (54.4)	29 (54.7)	32 (60.4)	30 (55.6)	.917
Age (years), mean ± SD	68.8 ± 10.4	72.6 ± 9.3	69.9 ± 9.1	71.7 ± 9.8	.159
Medical history, no. (%)					
Hyperlipemia	24 (42.1)	30 (56.6)	28 (52.8)	40 (74.1)	.008
Hypertension	28 (49.1)	20 (37.7)	29 (54.7)	34 (63.0)	.066
Diabetes mellitus	17 (29.8)	19 (35.8)	29 (54.7)	32 (59.3)	.004
Coronary heart disease	14 (24.6)	16 (30.2)	19 (35.8)	10 (18.5)	.212
Atrial fibrillation	9 (15.8)	3 (5.7)	7 (13.2)	6 (11.1)	.398
Prior stroke	9 (15.8)	6 (11.3)	2 (3.8)	13 (24.1)	.021
Smoking history, no. (%)	26 (45.6)	16 (30.2)	24 (45.3)	28 (51.9)	.137
Drinking history, no. (%)	12 (21.1)	14 (26.4)	13 (24.5)	14 (25.9)	.912
Laboratory findings, median (IQR)					
Leukocyte ($\times 10^9$/L))	7.1 (5.7–8.2)	6.3 (5.2–8.1)	7.5 (6.3–9.4)	8.7 (6.9–9.5)	<.001
Neutrophil (%)	65.3 (57.8–75.2)	71.3 (61.1–78.4)	75.7 (66.5–81.0)	71.1 (63.4–81.1)	.007
ESR (mm/h)	7.0 (5.0–11.0)	12.0 (6.0–17.0)	18.0 (8.0–24.5)	18.5 (12.0–25.3)	<.001
LDL-C (mmol/L)	2.06 (1.54–2.49)	2.44 (1.89–3.02)	2.58 (1.91–3.21)	3.20 (2.36–3.66)	<.001
HbA1C (%)	6.0 (5.7–6.4)	6.1 (5.6–7.3)	6.4 (5.9–7.7)	7.1 (6.2–8.1)	<.001
Stroke, no (%)	7 (12.3)	8 (15.1)	16 (30.2)	25 (46.3)	<.001

Hs-CRP values were divided into 4 levels by quartiles as follows: quartile 1 (Q1), <0.73 mg/L; quartile 2 (Q2), 0.73–1.50 mg/L; quartile 3 (Q3), 1.50–3.06 mg/L; and quartile 4 (Q4), >3.06 mg/L. ESR = erythrocyte sedimentation rate, HbA1c = glycated hemoglobin A1c, IQR = interquartile ranges, LDL-C = low-density lipoprotein cholesterol, SD = standard deviation.

Table 3

Univariate and multivariate logistic regression analysis for the association of high-sensitivity C-reactive protein with stroke.

Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male gender	4.463 (2.155–9.244)	<.001	5.635 (2.212–14.352)	<.001
Age	0.972 (0.942–1.004)	.084	0.987 (0.950–1.026)	.501
Hypertension	1.864 (1.000–3.476)	.050	1.710 (0.809–3.616)	.160
Diabetes mellitus	1.785 (0.967–3.296)	.064	1.172 (0.484–2.843)	.725
Smoking history	1.749 (0.948–3.227)	.074	0.641 (0.281–1.461)	.290
Hs-CRP (mg/L)		<.001		.027
Q1	1 (Ref)		1 (Ref)	
Q2	1.270 (0.426–3.782)	.668	0.912 (0.262–3.176)	.885
Q3	3.089 (1.154–8.268)	.025	1.867 (0.604–5.773)	.278
Q4	6.158 (2.370–15.999)	<.001	4.099 (1.272–13.216)	.018
Leukocyte $>10\times10^9$/L	2.891 (1.109–7.538)	.030	1.935 (0.586–6.387)	.278
Neutrophil >70%	2.532 (1.342–4.777)	.004	1.769 (0.822–3.806)	.144
ESR >20 mm/h	1.587 (0.812–3.103)	.177	–	–
LDL-C >2.6 mmol/L	4.074 (2.118–7.837)	<.001	2.543 (1.175–5.505)	.018
HbA1C >6.0%	2.419 (1.187–4.931)	.015	1.241 (0.446–3.451)	.679

CI = confidence interval, ESR = erythrocyte sedimentation rate, HbA1c = glycated hemoglobin A1c, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, Ref = reference.

* Adjusted for variables with a P value <.10 in univariate analysis, including gender, age, medical histories of hypertension and diabetes mellitus, smoking history, leukocyte, neutrophil, LDL-C, and HbA1C.

with AVS. This association was independent of other well-known influential factors of stroke such as age, gender, hypertension, and diabetes.

Hs-CRP is a sensitive indicator of inflammation and has evolved as an important marker of atherosclerosis. In our study, we firstly found that stroke patients with AVS had significantly higher level of hs-CRP than nonstroke patients, reflecting the potential involvement of inflammatory response. On the contrary, a recent study found no difference of CRP levels between stroke and nonstroke patients with AVS.[13] Notably, it was CRP, instead of hs-CRP, that was assessed in that study. Lower sensitivity of CRP compared with hs-CRP might to a large extent explain the discrepancy. Furthermore, our study demonstrated that stroke occurrence in patients with AVS increased in pace with increasing quartile levels of hs-CRP, supporting the correlation between hs-CRP and stroke. The following multivariate logistic regression analysis showed that higher level of hs-CRP remained an independent factor associated with stroke after adjusting for the confounders such as LDL-C or HbA1C, suggesting the distinctive role of hs-CRP in pathophysiological changes of stroke.

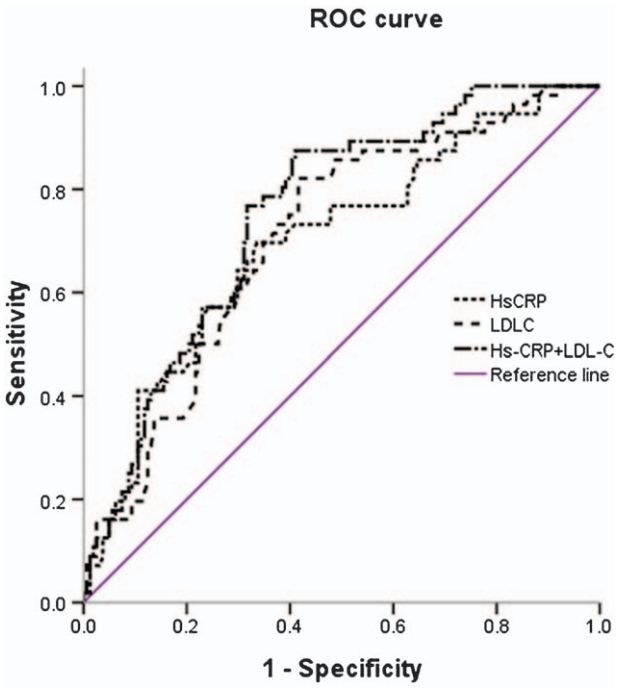

Figure 1. Receiver operating characteristic curve analysis. Receiver operating characteristic curve analysis for evaluation the diagnostic power of hs-CRP and LDL-C for stroke in patients with AVS on the basis of each biomarker alone and incorporating 2 biomarkers. AVS = acute vestibular syndrome, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, ROC = receiver operating characteristic.

Firstly, acute ischemic stroke in the early stage immediately evokes a quick inflammatory cascade which could be a consequence of Toll-like receptors activation following atherosclerotic plaque rupture and thromboembolic events.[14] Hs-CRP, as an acute phase reactant, is rapidly upregulated paralleled by changes in the levels of other cytokines such as interleukin 6 and tumor necrosis factor.[15] Moreover, hs-CRP levels were positively related to infarct volumes,[16] therefore, it may aid in the evaluation of severity of acute stroke as well as identification of stroke. Additionally, gradual development of atherosclerotic plaque is also strongly linked to inflammation. Growing evidence showed that elevated hs-CRP predicted first-ever ischemic stroke and recurrence of stroke. In our study hs-CRP level was assessed after symptom onset, hence the possibility that stroke patients with AVS had long-lasting higher level of hs-CRP before stroke onset, and were at a higher risk of stroke than nonstroke patients could not be excluded. With regard to the role of CRP, it is still elusive whether CRP is involved in the pathogenesis of atherosclerosis or is elevated as a response to atherosclerosis.[17]

Besides hs-CRP, we found that male gender and increased LDL-C were also significantly associated with stroke in patients with AVS. Similarly, some prior studies have showed that male patients with AVS were at higher risk for stroke than female.[18,19] However, the gender effect on the stroke risk was markedly attenuated by some confounders in another research.[20] One possible explanation for the discrepancies might be the difference in sample sizes and patients selection criteria.

With regard to LDL-C, in contrast to study from Zuo et al,[13] our finding indicated that higher LDL-C was correlated with stroke, it may be attributed to that elevated LDL-C could contribute to endothelial dysfunction, elicit inflammation, promote atherosclerosis, and exacerbate plaque burden. In previous literatures, the association between cholesterol and stroke risk is still controversial. No association was found between the cholesterol and the occurrence of stroke in the Framingham study,[21] whereas Glasser et al[22] revealed that LDL-C is significantly associated with incident ischemic stroke in REasons for Geographic And Racial Differences in Stroke study. The discordance of results could be due to the difference of the target population as well as the medication history of lipid-lowering drugs. Thus, the role of LDL-C in predicting stroke with AVS warrants intensive investigation in future.

Additionally, we found that hs-CRP had a great diagnostic value at 1.82 mg/L for stroke patients with AVS by ROC curve analysis. Combining hs-CRP with LDL-C improved the discriminatory ability. Interestingly, the threshold value of hs-CRP obtained from our study was almost identical with the data from a previous study which showed hs-CRP level at 1.72 mg/L in patients with SAO stroke subtype.[23] Meanwhile, consistent with a recent research,[20] the TOAST classification of stroke in patients with AVS in our study was primarily due to SAO. In view of the fact that hs-CRP levels differed in different stroke subtypes,[24] therefore, it is necessary to find the specific target value of hs-CRP for stroke patients with AVS.

Some limitations of our study should be noted. First, the present study was a retrospective study at a single center, and the sample population does not represent the general population. Future prospective studies with multicenter data and large sample size are needed to validate our findings. Second, although the time of admission for patients was restricted to 3 days after symptom onset, fluctuation of hs-CRP level could not be completely excluded. However, in stroke patients with mild outcome, the temporal profile of CRP during the first week after symptom onset was proved to be relatively stable.[25]

5. Conclusion

To our knowledge, this is the first study to report that hs-CRP was independently associated with stroke in patients with AVS. Elevated level of hs-CRP ($\geq$1.82 mg/L) may be a useful indicator of stroke in patients with AVS.

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