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Original article

Aspirin resistance are associated with long-term recurrent stroke events after ischaemic stroke

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ABSTRACT

Objective: To investigate the prevalent of aspirin resistance (AR) in stroke and its association with recurrent stroke in 214 patients with ischemic stroke who were receiving aspirin before the stroke onset.
Methods: Two hundreds and fourteen acute stroke patients who previously received aspirin therapy (100 mg/day for ≥7 days) were enrolled. Whole blood samples were collected for platelet aggregation testing. The result is expressed in aspirin reaction units (ARU). A cutoff of 550 ARU was used to determine the presence of AR. A follow-up period of 1 year was performed to record stroke recurrence events.
Results: In this study, the median age was 68 years (IQR, 60–77 years), and 118 (55.1%) were men. A total of 43 of 214 enrolled patients (20.1%) were AR. ARU levels were significantly higher in patients with recurrence than those without (514[IQR: 466–592] *vs.* 454[IQR: 411–499]; P < 0.001). The stroke recurrence distribution across the ARU quartiles ranged between 7.41% (first quartile) to 40.74% (fourth quartile). In multivariate analyses, the 3th and 4th quartile of ARU was significantly associated with stroke recurrence during the observation period compared to the 1 st quartile group, and the adjusted risk increased by 215% (OR = 3.15 [95% CI 1.96–4.33], P = 0.007) and 322% (4.22[2.56–7.16], P < 0.001). In multivariate logistic regression analysis, AR was associated with a higher risk of stroke recurrence, and the adjusted risk increased by 365% (OR = 4.65; 95% CI = 2.99–8.16; P < 0.001).
Conclusion: In conclusion, AR is not uncommon in Chinese stroke patients who receive anti-platelet medications. Patients with AR may have a greater risk of suffering stroke recurrence events.

1. Introduction

Aspirin is the cornerstone of anti-platelet therapy in cardiovascular medicine today. It is widely used in the treatment of stroke. It significantly reduces the risk of recurrence (Antithrombotic Trialists Collaboration, 2002), severity of stroke (Wilterdink et al., 2001; Sanossian et al., 2006) and infarct growth (Ovbiagele et al., 2008).

However, a proportion of patients treated with aspirin demonstrate poor clinical outcomes, which may be attributable to aspirin resistance (AR, Hankey and Eikelboom, 2004). Aspirin resistance is the failure of aspirin to reduce platelet production of thromboxane A2 and therefore platelet activation and aggregation (Hankey and Eikelboom, 2006). Approximately 30% of patients with stroke do not achieve an expected level of platelet inhibition with aspirin (Bennett et al., 2008).

These “aspirin-resistant” patients exhibit an increased risk of vascular events such as myocardial infarction, transient ischemic attack, or stroke (Ozben et al., 2010). Some patients with AR exhibit an increased risk of recurrent stroke (Snoep et al., 2007) and poor clinical outcomes (Kim, 2015). Thus, we hypothesize that AR is associated with future stroke recurrence events in ischemic stroke (IS) patients. In this study, we performed platelet aggregation testing to determine the presence of AR and to investigate the association between AR and stroke recurrence events in a cohort of patients with an acute IS (AIS) who were receiving aspirin during a 1-year follow-up period.

2. Material and methods

2.1. Methods

From January 2014 to December 2015, consecutive first-ever AIS patients admitted to the Department of Emergency of the Xinxiang Central Hospital, China, were identified. The inclusion criteria were (1) at least 7 days of aspirin therapy (acetylsalicylic acid, 100 mg daily) prior to stroke onset; (2) evidence of ischemic infarct on magnetic

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Table 1
Baseline characteristics of stroke patients with AR and without AR.

	ALL	Patients with AR[ξ]	Patients without AR
N	214	43	171
Age (years), median(IQR)	68(60–77)	70(62–78)	68(59–76)
Male sex, n (%)	118(55.1)	24(55.8)	94(55.0)
BMI (kg/m2), median(IQR)	27.6(24.9–29.2)	27.9(25.1–29.3)	27.5(24.8–29.2)
Median NIHSS score at admission	8(3–14)	13(8–18) [†]	6(2–11)
Lesion volumes(ml, N = 135), (median, IQR)	10.8(4.9–20.4)	16.8(8.4–31.5) [†]	8.2(4.1–16.4)
Time from onset to ARU test(hours), median(IQR)	14.0(7.0–16.0)	14.5(8.0–17.0)	13.7(6.5–15.5)
Vascular risk factors, n (%)			
Hypertension	144(67.3)	28(65.1)	116(67.8)
Diabetes mellitus	77(36.0)	16(37.2)	61(35.7)
Hypercholesterolemia	71(33.2)	15(34.9)	56(32.7)
Coronary heart disease	63(29.4)	17(39.5)	46(26.9)
History for TIA	40(18.7)	11(25.6)	29(17.0)
Current cigarette smoking	51(23.8)	12(27.9)	39(22.8)
Current drinking	41(19.2)	20(23.3)	31(18.1)
Systolic blood pressure(mmHg), median(IQR)	145(130–160)	150(135–168)	142(126–157)
Pre-stroke treatment, n (%)	135(63.1)	31(72.1)	104(60.8)
Administration of IV-tPA, n (%)	26(12.1)	7(16.3)	19(11.1)
Stroke syndrome, n (%)			
TACS	47(22.0)	11(25.6)	36(21.1)
PACS	73(34.1)	11(25.6)	62(36.3)
LACS	53(24.8)	16(37.2) [†]	37(21.6)
POCS	41(19.2)	5(11.6)	36(21.1)
Stroke etiology no. (%)			
Small-vessel occlusive	38(17.8)	9(20.9)	29(17.0)
Large-vessel occlusive	42(29.6)	7(16.3)	35(20.5)
Cardioembolic	81(37.9)	19(44.2)	62(36.3)
Other	23(10.7)	5(11.6)	18(10.5)
Unknown	30(14.0)	3(7.0)	27(15.8)
Laboratory findings, median(IQR)			
Total cholesterol, mmol/l	4.08(3.31 − 4.89)	4.08(3.33–4.93)	4.08(3.30–4.88)
Triglycerides, mmol/l	1.42(1.15–1.95)	1.44(1.19–2.01)	1.41(1.14–1.94)
High–density lipoproteins, mmol/l	1.37(1.05–1.69)	1.40(1.08–1.75)	1.36(1.04–1.66)
Low-density lipoproteins, mmol/l	2.11(1.20–2.82)	2.44(1.38–2.99) [†]	2.04(1.12–2.67)
FBG, mmol/l	5.68(4.94–6.73)	6.15(5.43–7.12) [†]	5.43(4.76–6.49)
Hs–CRP, mg/dl	0.48(0.27–0.94)	0.64(0.43–1.54) [†]	0.35(.21–0.69)
HCY, umol/l	17.4(12.5–20.6)	17.8(12.6–20.9)	17.3(12.5–20.5)
PLT, $x10^3$/ml	179(138–244)	183(140–248)	178(137–243)

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; TPA-T: Tissue plasminogen activator-treated; LACS, lacunar syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome; Hs-CRP, high sensitivity C-reactive protein; FBG, fasting blood glucose; HCY, homocysteine; PLT, Platelet; ARU, aspirin reaction units; AR, aspirin-resistant.

[†] $P < 0.05$ when compare with the group of patients without AR.

[ξ] AR was defined by more than 550 ARU.

resonance imaging (MRI) and/or CT; (3) within 24 h of experiencing a new focal or global neurological event; (4) with informed consents. Patients with malignant tumor, head trauma, severe edema, renal insufficiency (creatinine > 1.5 mg/dl), acute or chronic inflammatory disease and autoimmune diseases were excluded. Patients who lost blood samples and follow-up were also excluded. The present study has been approved by the ethics committee of the Xinxiang Central Hospital. Written informed consents were obtained from participants or their relatives.

Clinical information was collected. Demographic data (age and sex), body mass index (BMI), and history of risk factors (hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, smoking habit and alcohol abuse) were obtained at admission. Pre-stroke therapy (oral anticoagulants and antihypertensive treatment) and acute treatment (IV thrombolysis and/or mechanical thrombectomy) was recorded. Clinical severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS). Strokes were classified according to the criteria of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. The clinical stroke syndrome was determined applying the criteria of the Oxfordshire Community Stroke Project (OCSP). MRI with diffusion-weighted imaging (DWI) was available in some patients. The infarct volume was calculated by using the formula $0.5 \times a \times b \times c$ (Sims et al., 2009).

From every patient 2 ml blood samples were drawn into tubes containing 3.2% citrate 1–4 h at first morning after admission under fasting. Aspirin-induced platelet inhibition was measured using a commercially available point-of-care device, the Ultegra Rapid Platelet Function Assay-ASA (the VerifyNow System, Accumetrics, San Diego, California). The result is expressed in aspirin reaction units (ARU). In line with previous definitions, a cutoff of 550 ARU was used to determine the presence of AR (Zheng et al., 2013). An ARU value of ≥550 IU was defined as AR, while < 550IU was defined as aspirin sensitive (AS). Raw ARU scores as continuous variables were also used to indicate the degree of platelet aggregation (Ozben et al., 2011). Results of the other blood analyses, such as C-reactive protein (CRP), fasting blood glucose (FBG), homocysteine (HCY), Platelet, Total cholesterol, LDL cholesterol and white blood count (WBC) were also measured using routine laboratory methods. The investigators were blinded to the results of aspirin resistance when whey obtained the clinical information.

We followed the participants for a median of 1 year using a standard questionnaire, and telephone or household contact by physician investigators every 4 months after admission. The primary end-point was stroke recurrence among 1-year after stroke onset. The secondary endpoint was death from any cause. Stroke recurrence was defined as sudden functional deterioration in neurological status with decrease of NIHSS score of 4 or more, or a new focal neurological deficit of vascular origin lasting > 24 h (Huang et al., 2016). An early recurrent stroke (< 7 days) also was included into analyses.