

Detrimental effects of intracerebral haemorrhage on patients with CADASIL harbouring NOTCH3 R544C mutation

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) caused by mutations of the 33-exon *NOTCH3* gene is the most common single gene disorder of stroke.¹ To date, more than 200 different *NOTCH3* mutations have been reported worldwide, while R544C in exon 11 was the most prevalent hot spot mutation in East Asia and accounted for more than 70% of the patients in their CADASIL cohorts.^{2,3} Patients with CADASIL may suffer from ischaemic stroke (IS) and intracerebral haemorrhage (ICH), especially among Asians. Therefore, we aimed to compare the clinical features of acute ICH vs IS events in patients with CADASIL and focused on the effects of ICH on stroke recurrence and long-term outcome.

METHODS

The patients enrolled in this study were prospectively recruited from a multicentre stroke registry established since 2006 with at least 12 hospitals in Taiwan. We screened R544C mutation from participants who provided their blood sample and those whose harbouring R544C mutation were then included in the present study. Preadmission, inpatient and discharge data were collected by trained personnel. The responsible neurologist on each study site will examine the medical record or interview the patients to acquire follow-up information. All patients received at least one neuroimaging examination to document the locations of acute stroke. Abnormal white matter hyperintensity

(WMH) lesion was scored by the Fazekas scale. The number and distribution of cerebral microbleeds (CMBs) were also documented.

Clinical and neuroimaging features were compared using the t-test, Mann-Whitney U test and χ^2 test when appropriate. Kaplan–Meier plots of recurrent stroke survival were computed for the ICH-onset versus IS-onset groups and compared with the log-rank test. A Cox proportional hazards regression model was then used to estimate the HR and 95% CI for recurrent stroke.

RESULTS

From the registry consisting of nearly 2000 stroke patients, 71 (mean age at first stroke, 58.39.6 years; 63% male) were screened positive for R544C mutation, and 103 stroke events of them were documented (37 ICH and 64 IS events). The initial stroke severity, functional outcome at discharge, and mortality were significantly higher in the ICH events. The mean ICH volume was 10.9 ml, and the most common locations of ICH were thalamus (51%) and basal ganglia (27%). Among the IS events, subcortical white matter was the predominant stroke location (41%), and small vessel occlusion type accounted for more than half (59%) of stroke cases.

Of 67 patients with a median follow-up time of 66 months (IQR, 39–106), 21 (31%) patients were classified as ICH-onset, 29 patients had recurrent strokes and 10 patients died. Patients with ICH-onset were more likely to have high family burden of stroke (at least two first-degree relatives with stroke), slightly higher WMH score and higher total CMBs count (table 1). The annual stroke recurrence rate was 8.1 per 100 person-years (95% CI 5.6 to 11.3) in all patients and was higher in the ICH-onset than IS-onset group (10.9 vs 7.0 per 100 person-years, log-rank=0.03; online supplementary figure 1). The recurrent type of stroke may be either haemorrhagic or ischaemic or even both. After adjustment for age at first stroke, gender and hypertension, patients with ICH-onset still carried a higher risk of recurrent stroke (HR 2.17, 95% CI 1.01 to 4.64, p=0.05). Overall, 28 (42%) patients suffered from at least one ICH events. Patients with ever ICH had significantly higher mortality rate, family burden of stroke, WMH lesion, and more CMBs count than those with IS-only (online supplementary table 1).

Table 1 Clinical and neuroimaging features of patients with CADASIL with ICH-onset vs IS-onset

	ICH-onset (n=21)	IS-onset (n=46)	P values
Age (at first stroke)	58.3±9.1	57.8±9.9	0.85
Male	14 (66.7)	28 (60.9)	0.65
Annual recurrent rate	10.9/100 person-years	7.0/100 person-years	0.03*
Recurrence stroke	12 (57.1)	17 (37.0)	0.12
Only IS	5	10	0.66
Only ICH	6	6	
Both ICH and IS	1	1	
Mortality	6 (28.6)	4 (8.7)	0.06
Family history of stroke	11 (52.4)	19 (41.3)	0.40
High family burden of stroke	7 (33.3)	5 (10.9)	0.03
Hypertension	19 (90.5)	36 (78.3)	0.23
Diabetes mellitus	6 (28.6)	13 (28.3)	0.98
Hyperlipidaemia	12 (57.1)	22 (47.8)	0.48
Smoking	7 (33.3)	20 (43.5)	0.43
WMH score†	2.9±0.3	2.6±0.7	0.16
Anterior temporal WMH	1 (8.3)	5 (11.4)	0.99
External capsule WMH	10 (83.3)	30 (68.2)	0.48
Numbers of lacunes	5.2±4.7	6.3±5.9	0.58
Number of CMBs‡	27.4±23.8	12.5±17.5	0.05
Location of CMBs: none	0	8	0.14
Pure deep	1	6	
Pure lobar	0	1	
Mixed	8	13	

Data were presented by count number (percentage) or mean SD.

*Compared with log-rank test.

†Only 56 patients (12 in ICH, 44 in IS group) had available MRI.

‡Only 37 patients (9 in ICH, 28 in IS group) had available CMBs imaging.

CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarct and leukoencephalopathy; CMBs, cerebral microbleeds; ICH, intracerebral haemorrhage; IS, ischaemic stroke; WMH, white matter hyperintensity.

DISCUSSION

The present study demonstrated that up to 40% patients with CADASIL harbouring R544C mutation could develop ICH during the follow-up course. The impacts of ICH on functional outcome were huge and included increased risk of stroke recurrence and mortality. The risk factors for ICH identified in these patients were strong family history of stroke and severe white matter changes on neuroimaging.

There were several novel findings from our study. First, we described 37 ICH events on 28 patients of CADASIL, which is by far the largest case series to date. Apart from scatter case reports, one recent Korea study reported 22 ICH events out of 16 patients and another Taiwan study presented 18 cases of clinical or neuroimaging history of ICH.^{3,4} Interestingly, all these studies came from area where R544C mutation was prevalent. Second, a substantial high proportion (up to 30%) of patients had ICH as their initial presentation, and they were prone to have recurrent stroke and higher risk of mortality. This finding also implied that clinicians should consider the possibility of CADASIL even in patients with ICH, especially when

they had strong family history of stroke, severe WMH lesion or high burden of CMBs. In addition, the prevalence of hypertension was high in our group, and the most common locations of ICH were also compatible with typical hypertensive haemorrhage. Whether a specific R544C phenotype of CADASIL vasculopathy, or a superimposed hypertensive arteriopathy, was responsible for the occurrence of ICH required further investigation.^{4,5}

There were limitations of our study. First, patients recruited from the stroke registry were only screened for R544C mutation because it accounted for more than 70% of *NOTCH3* mutation in Taiwan. Consequently, our findings may not be applicable to other mutation sites of *NOTCH3* or other populations. Second, our study included patients with stroke only. Patients with CADASIL without stroke but with other manifestations were not included, thus we could not identify crucial background factors related to the occurrence of stroke.

In conclusion, the present study found ICH events in a high proportion of patients with CADASIL with *NOTCH3* mutation R544C. Subjects with ICH as their first

stroke event had significantly higher risk of recurrent stroke and mortality. Further study to determine the appropriate management of patients with CADASIL is essential to both preventing ischaemic and avoiding haemorrhagic events.

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