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REVIEW ARTICLE

Intracerebral hemorrhage in CADASIL

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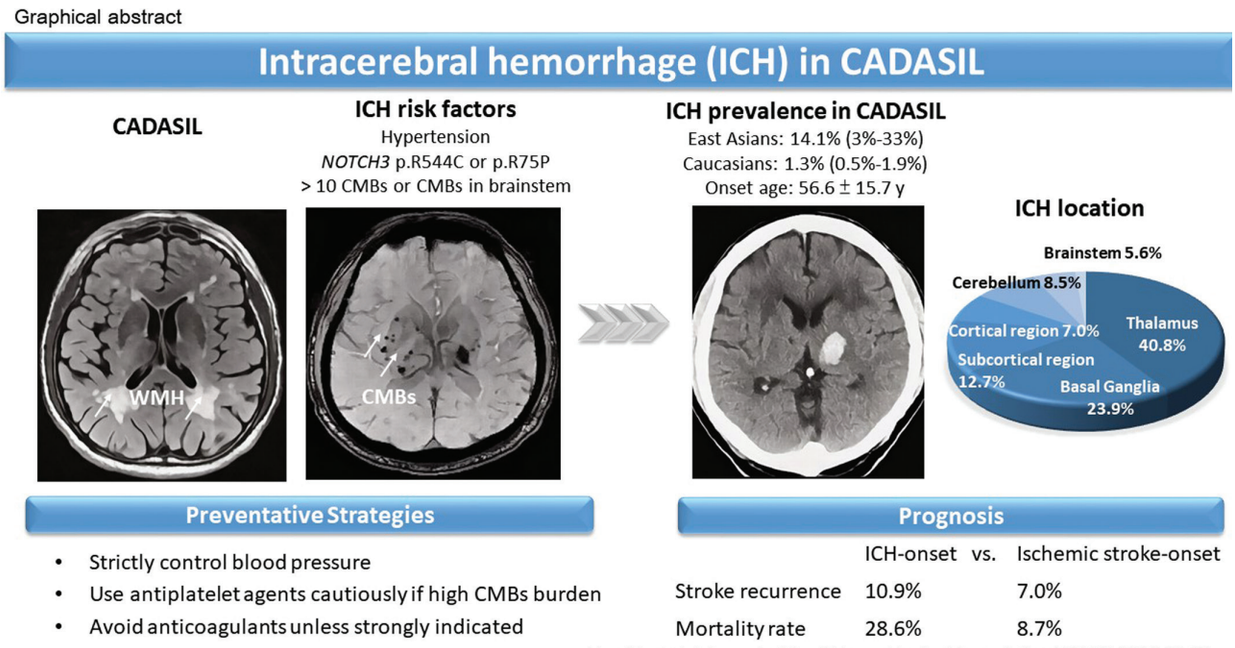
Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common hereditary cerebral small vessel disease caused by mutations in the *NOTCH3* gene. This review highlights the increasing recognition of intracerebral hemorrhage (ICH) as a significant manifestation of CADASIL, often predominantly characterized by ischemic strokes and vascular dementia. Recent studies indicate that the prevalence of ICH in CADASIL patients ranges from 0.5% to 33.3%, the variability of which is mainly influenced by ethnicity. In East Asian cohorts, specific *NOTCH3* mutations like p.R544C and p.R75P are more prevalent and have been associated with a higher rate of ICH, suggesting a link between these mutations and the hemorrhagic risk. Hypertension, as with other etiologies of ICH, is a key risk factor in CADASIL patients, with 40% to 90% of those who experience ICH also having a history of hypertension. The presence of cerebral microbleeds (CMBs) and a high CMB load are strongly associated with an increased risk of ICH. Neuroimaging studies show that ICH in CADASIL patients predominantly occurs in the thalamus and basal ganglia. There is a notable spatial correlation between CMBs and subsequent ICH, suggesting that CMBs may serve as markers of microangiopathy in regions prone to vascular injury. CADASIL patients with ICH experience greater morbidity, higher mortality rates, and increased annual stroke recurrence risk compared with those with ischemic events. In summary, this review emphasizes the need for tailored management strategies that prioritize rigorous blood pressure control and the careful use of antithrombotic agents in CADASIL patients with a high burden of CMBs. By advancing our understanding of ICH in CADASIL, we aim to improve diagnostic and therapeutic approaches, ultimately enhancing patient outcomes and quality of life in this high-risk population.

Keywords: CADASIL; Cerebral small vessel disease; Intracerebral hemorrhage; *NOTCH3* gene

Graphical abstract



1. INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most prevalent hereditary cerebral small vessel disease (CSVD).[1,2] It is usually caused by cysteine-altering variants in the *NOTCH3* gene, which lead to the accumulation of granular osmiophilic material in the basement membrane of vascular smooth muscle cells and pericytes, contributing to the progressive degeneration of small vessels in the brain.[3,4] This vascular pathology manifests as a variety of neurological symptoms, including recurrent ischemic strokes, cognitive declines of varying severity, psychiatric disturbances, and migraine with aura.[5] Magnetic resonance imaging (MRI) studies typically reveal diffuse white matter hyperintensities (WMHs), lacunes, cerebral microbleeds (CMBs), and brain atrophy, which reflect the underlying small vessel pathology associated with CADASIL.[6]

CADASIL has traditionally been associated with ischemic strokes and vascular dementia, but recent studies have highlighted the increasing recognition of intracerebral hemorrhage (ICH) as a potential presentation of the disease.[7–9] Although ICH is often linked to hypertension and anticoagulation therapy, emerging evidence suggests that its prevalence in CADASIL may be higher than previously recognized, with many cases likely undiagnosed.[10–15] Notably, ICH carries a higher risk of morbidity and mortality compared to ischemic strokes, and several fatal cases in CADASIL patients with ICH have been reported.[7,13,16–18] This underscores the importance of identifying individuals at risk for ICH, as tailored strategies, such as careful antithrombotic therapy and optimal blood pressure (BP) management, could play a crucial role in mitigating these risks.

This review will explore the clinical implications of ICH in CADASIL, focusing on its prevalence, associated risk factors, and clinical and neuroimaging characteristics. In addition, we will discuss potential management strategies aimed at improving outcomes and enhance our understanding of ICH within the context of hereditary CSVD. By highlighting this critical issue, we aim to foster a more comprehensive approach to the diagnosis and management of ICH in patients with CADASIL.

2. THE PREVALENCE OF ICH IN CADASIL

Excluding one study that reported an ICH prevalence of 41.8% among 71 CADASIL patients identified from a cohort of 2000 patients with ischemic or hemorrhagic stroke,[11] the prevalence of ICH among cohorts primarily investigating patients with CADASIL ranged from 0.5% to 33.3% (Table 1).[12,15,19–28] When stratifying the subjects according to their ethnicities, 96 of the 681 CADASIL patients from the East Asian populations had ICH and 21 among the 1656 Caucasian CADASIL patients suffered from ICH (14.1% vs 1.3%). The significantly higher risk of ICH in CADASIL patients of East Asian descent may reflect the generally higher prevalence of ICH in the East Asian population compared to individuals of European ancestry.[29] Ethnicity might attribute to the increased risk for ICH among CADASIL patients in East Asian cohorts.

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A study conducted in the United Kingdom, which included 544 CADASIL patients, identified ICH in 10 individuals, indicating an ICH prevalence of 1.9%. In these cases, *NOTCH3* mutations were identified as p.R141C (2/10), p.R182C (2/10), p.C245S (1/10), p.R427C (1/10), p.R449C (1/10), p.C516F (1/10), and p.R558C (2/10).[15] Analogously, a multinational cohort from Germany and France,[26] comprising 369 CADASIL patients, revealed that while 227 (61.5%) had a history of stroke, only two individuals (0.5%) had experienced ICH. During a median follow-up period of 39 months, 69 patients suffered from ischemic stroke, yet no cases of ICH was observed. In contrast, the prevalence of ICH is obviously higher in the East Asian cohorts. A study of 94 genetically confirmed CADASIL patients in South Korea reported 22 instances of ICH in 16 patients (17%), all of whom carried the *NOTCH3* p.R544C mutation.[21] In addition, a cohort of 127 Han Chinese patients in Taiwan revealed that 27 (21.3%) had ICH lesions detected on brain susceptibility-weighted imaging or T2*-gradient-recalled echo images, with the most frequent *NOTCH3* mutation being p.R544C (22/27), followed by p.C222S (1/27), p.Y258C (1/27), p.R427C (1/27), p.R587C (1/27), and p.C977S (1/27).[12] These findings underscore the higher prevalence of ICH among CADASIL patients in East Asia.

It remained unclear whether the observed differences in ICH risks among CADASIL patients of different ethnic groups are partially attributed to specific *NOTCH3* mutations. *NOTCH3* p.R544C is the most common cause of CADASIL in both Taiwan and Jeju Island, South Korea.[30,31] Liao et al[32] reported that *NOTCH3* p.R544C is present in 70.5% of CADASIL pedigrees in Taiwan, with an ICH ratio of 16.2% in the cohort. In the CADASIL cohort on Jeju Island, 94 genetically confirmed individuals from 76 unrelated families were enrolled, with 89 (95%) carrying the p.R544C mutation and a prevalence of ICH of 17%.[21] Moreover, the *NOTCH3* p.R75P mutation is a common cysteine-sparing mutation in the East Asian population.[24,33] Ishiyama et al[34] demonstrated a significant association between this mutation and hemorrhagic phenotypes in both Japanese and Korean cohorts. In contrast, CADASIL in Caucasians and other ethnic groups shows a broad spectrum of *NOTCH3* mutations associated with ICH, with three cases in p.R133C and p.R182C, two cases in R141C, R169C, R558C and R1231C, and single case in other fifteen mutations (Fig. 1). Therefore, in addition to ethnic differences, the distinct genotype distribution in East Asian populations may play an additional role in the susceptibility of Asian CADASIL patients to ICH.

3. RISK FACTORS OF ICH IN CADASIL PATIENTS

A history of hypertension and a higher burden of CMBs are the most significant risk factors for ICH in CADASIL.[14] In contrast, traditional risk factors for sporadic ICH, such as advanced age, male sex, excessive alcohol consumption, and low cholesterol, seem not to influence ICH risk in CADASIL patients.[29] Hypertension is the most well-recognized risk factor for ICH in the general population.[29,48] A recent systematic review and meta-analysis involving 26 174 patients with ICH from 42 studies revealed that hypertension significantly increases the risk of both nonlobar and lobar ICH, with a double impact on nonlobar ICH.[49] Hypertension is able to promote arteriolosclerosis in small cerebral arteries, resulting in pathological changes such as fibrinoid necrosis, lipohyalinosis, microatheromas, and microaneurysms.[50] It would weaken the vessel walls and increase the risk of vessel rupture, especially in CSVD, such as CADASIL. In CADASIL cohorts, the prevalence of hypertension ranged from 23% to 53.2%.[12,20–28,51,52] In a UK cohort, 10 patients with various *NOTCH3* mutations and ICH were identified, 40% of whom had hypertension.[15] However, a meta-analysis combining

Table 1

Characteristics of CADASIL cohorts with ICH

Study	Country	Ethnicity	Cohort size	Number of ICH cases	ICH location[a]	Common *NOTCH3* mutations	Male, % (total/ICH)	Hypertension, % (total/ICH)	Presence of CMB, % (total/ICH)
Chen et al[19]	China	Han Chinese	169	5 (3%)	NA	p.R607C (18.9%) p.R544C (15.4%)	57.4/NA	NA/NA	NA/NA
Min et al[20]	Korea	Korean	142	9 (6.3%)	NA	p.R544C (20.4%) p.R75P (15.5%)	38.7/NA	28.2/NA	NA/NA
Liao et al[12]	Taiwan	Han Chinese	127	27 (21.3%)	Tha (12); Lobar (11); CR (5); Ce (5); Br (2); BG (2)	p.R544C (77.2%)	48/55.6	52.8/74.1	74/100
Lee et al[21]	Korea	Korean	94	16 (17%)	BG (9); Tha (5); Lobar (4); Ce (2); Br (2)	p.R544C (94.7%)	55.3/NA	53.2/NA	66/NA
Chen et al[22]	Taiwan	Han Chinese	63	21 (33.3%)	Tha (12); BG (7); Lobar (1); CR (1)	p.R544C (92.1%)	63.5/66.7	27/81	79.2/100
Tan et al[23]	China	Han Chinese	52	12 (23.1%)	NA	p.R544C (23.1%) p.R90C (13.5%)	53.8/NA	40/58.3	NA/NA
Kim et al[24]	Korea	Korean	34	6 (17.6%)	BG (3); Tha (2); CR (1)	p.R75P (14.7%) p.R544C (11.8%) p.Y465C (11.8%)	35.3/NA	41.2/50	54.8/33.3
Sukhonpanich et al[15]	UK	Caucasian	516	10 (1.9%)	BG (9); Lobar (4); Tha (2); Br (1); Ce (1)	p.R141C (20%) p.R182C (20%) p.R558C (20%)	42.8/50	24.4/40	45.2/50
Dupe et al[25]	France	Caucasian	446	6 (1.4%)	Br (6)	NA	44.2/NA	28/NA	36.3/NA
Puy et al[26]	Germany + France	Caucasian	369	2 (0.5%)	NA	NA	44.7/NA	24.1/NA	35.5/NA
Adib-Samii et al[27]	UK	Caucasian	200	1 (0.5%)	Br (1)	p.R141C (20.2%) p.R169C (16%) p.R182C (14%)	43/NA	23.5/NA	NA/NA
Nannucci et al[28]	Italy + UK	Caucasian	125	2 (1.6%)	Tha-capsular (2); Ce (1)	NA	44.8/NA	29.6/100	34.4/100

BG = Basal ganglia; Br = Brainstem; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Ce = Cerebellum; CR = corona radiate; ICH = intracerebral hemorrhage; NA = not available; Tha = thalamus.

[a]The number in parentheses indicates the number of case.

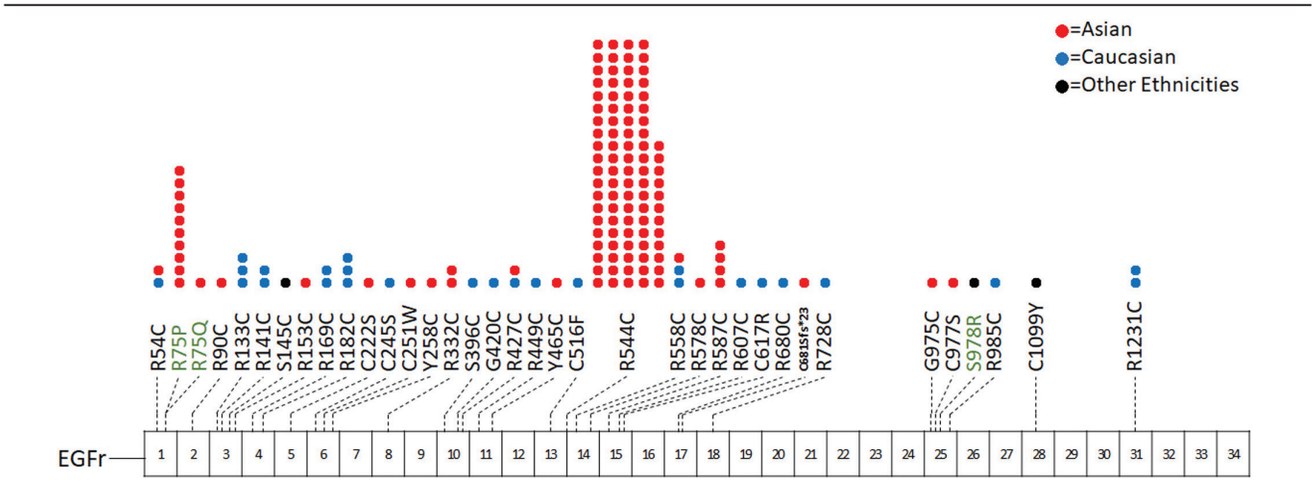

Fig. 1 *NOTCH3* mutations in CADASIL patients with ICH in literature. This schematic diagram illustrates the reported CADASIL-ICH cases and the associated mutations on the 34 EGFr domains of the NOTCH3 protein.[7,9,10,12,13,15,21,24,34–47] Each filled circle represents a single CADASIL patient with a specific *NOTCH3* mutation associated with ICH. The color of the circle denotes patient ethnicity, with red for Asian, blue for Caucasian, and black for other ethnicities. Cysteine-sparing mutations are highlighted in green. CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; EGFr = epidermal growth factor-like repeat; ICH = intracerebral hemorrhage.

these 10 patients with an additional 119 cases of various ethnicities revealed that 71.1% of them had hypertension, a proportion significantly higher than that observed in other CADASIL cohorts. Moreover, another study found that over 90% of ICH cases with the *NOTCH3* p.R544C variant in a Taiwanese cohort had hypertension.[11] Notably, in these cohorts, p.R544C carriers experienced an older age of symptom onset compared to other mutation carriers (58.3 ± 9.1 years vs 53.3 ± 7.2 years). In a recent study involving 1080 individuals carrying *NOTCH3* p.R544C identified from 110 000 participants enrolled in the

Taiwan Biobank, hypertension was found to be associated with an increased risk of stroke.[53] Therefore, hypertension may have a synergist effect with *NOTCH3* mutations on vascular damage, resulting in more severe CSVD and a greater risk of ICH.

CMBs are small (less than 10 mm in diameter), focal, perivascular hemosiderin depositions, which result from damages to the cerebral small vessels.[54] In patients with stroke, CMBs have been reported to be strongly correlated with the occurrence of ICH, particularly the locations of CMBs in the lobar area or deep brain structure being associated with ICH present in the same regions.[55] In CADASIL cohorts, the presence of CMBs was reported in 34.4% to 79.2% of patients;[12,15,21,22,24–26,28,56] however, among CADASIL patients with ICH, CMBs may be detected in over 90% of the subjects,[12,28,30] highlighting the close relationship between CMBs and ICH. Liao et al[12] found that 85.2% of CADASIL patients with ICH had more than 10 cerebral CMBs, whereas only 39% of those without ICH did. They found that the presence of CMBs in the brainstem and a total CMB count >10 were associated with 5.8- and 3.8-fold increased risk of ICH in patients with CADASIL, respectively. These findings suggest that CMBs may be considered as pre-hemorrhagic lesions and an important risk factor for ICH.

Antiplatelet agents, especially acetylsalicylic acid, are widely used for the secondary prevention of ischemic stroke.[57] They are generally not associated with a heightened risk of ICH in CADASIL patients or the general population in most observational studies.[58] A retrospective study of 455 patients with CADASIL, including 40 (8.8%) receiving antiplatelet agents, found no significant impact of antiplatelet use on ICH incidence.[59] Similarly, in a UK case series of 544 CADASIL patients, 10 experienced ICH, with no increase in ICH risk among those using antiplatelet agents; however, a significant increase in risk was observed in those taking anticoagulants.[15] Nonetheless, pooled follow-up data from 768 antithrombotic users revealed that the presence of CMB at baseline significantly increased the risk of subsequent ICH.[60] Therefore, in CADASIL patients with a high burden of CMB, the use of antithrombotic agents should be approached with caution, given that the risk of ICH in this subgroup may be elevated.

4. CLINICAL AND NEUROIMAGING CHARACTERISTICS OF ICH IN CADASIL

In the general population, the incidence of ICH increases with age.[61] A recent study of an inpatient database in the Netherlands reported that the rate of ICH per 100 000 people was 5.9 for those aged 35 to 54 years, 37.2 for those aged 55 to 74 years, and 176.3 for individuals aged 75 to 94 years, highlighting significant age-dependent features.[62] In patients with CADASIL, ICH typically occurs at an average age of 56.6 ± 15.7 years, with a higher prevalence in males (57.4%).[15] This suggests that CADASIL may lead to an earlier onset of ICH compared to the general population.

In CADASIL patients, deep brain regions are the most common locations for ICH.[14] A review of 142 ICH lesions among 129 CADASIL patients revealed that the thalamus was the most common site of ICH (58 lesions, 40.8%), followed by the basal ganglia (34 lesions, 23.9%), subcortical white matter (18 lesions, 12.7%), cortical regions (10 lesions, 7.0%), cerebellum (12 lesions, 8.5%), and brainstem (8 lesions, 5.6%).[15] Interestingly, the thalamus was also the most common location for CMBs.[10,12,35] Previous study have identified a close spatial association between CMBs and subsequent ICH, particularly in the putamen and thalamus, suggesting that CMBs may indicate microangiopathy that poses an increased likelihood of hemorrhage.[63]

The clinical manifestations of ICH are determined by the size and location of the hemorrhage. A supratentorial ICH that affects the basal ganglia or thalamus may lead to contralateral sensorimotor deficits. In terms of lobar hemorrhages, symptoms may include high cortical dysfunctions such as aphasia, hemianopia, gaze deviation, and neglect.[29] Other typical symptoms that differ from those of ischemic stroke include headache, nausea or vomiting, and decreased levels of consciousness, which are associated with raised intracranial pressure.[48] The clinical presentations of ICH in CADASIL are similar to those of sporadic ICH. In patients with CADASIL and ICH, hemiparesis is the most frequently observed manifestation that has been reported in approximately 60% of cases, reflecting that the thalamus and basal ganglia are the most common sites of hemorrhage. In addition, altered mental status and headache were observed in about one-third of patients, which may be associated with those who had a larger hematoma.[15] Seizures were observed in approximately 10% of CADASIL patients with ICH, a proportion comparable to that seen in ICH cases in the general population.[64]

Although ICH occasionally can be life-threatening, several studies have indicated that some hemorrhagic lesions were "silent" in CADASIL patients.[9,12,13,21,36] In a study involving 127 patients with CADASIL who underwent susceptibility-weighted imaging or T2*-gradient-echo imaging, 37 ICH lesions were identified, of which 22 were asymptomatic.[12] This suggests that the actual incidence of ICH could be underestimated, as asymptomatic lesions may remain undetected without MRI with heme-sensitive sequences. Moreover, among these asymptomatic lesions, lobar hemorrhage was most commonly encountered.[9,36] Notably, patients with both asymptomatic and symptomatic ICH lesions may show similar severity of WMH and lacunes, suggesting that they could have a comparable disease burden, including recurrent hemorrhagic and ischemic strokes.[12] This finding highlights the importance of including heme-sensitive sequencing in the assessment of CADASIL patients.

The presence of ICH not only indicates a focal vascular lesion but also reflects a greater burden of underlying pathological changes of CSVD. CADASIL patients with ICH often demonstrate more pronounced neuroimaging abnormalities associated with CSVD (Fig. 2). Palazzo et al[13] reported five CADASIL patients with ICH and included an additional 47 subjects with both CADASIL and ICH from a literature review. They found that all patients had extensive WMHs, and the majority of them also had CMBs and lacunar infarcts.[13] Chen et al[35] further compared neuroimaging markers between 45 ICH patients with *NOTCH3* mutations and 109 patients with sporadic ICH. Their study showed that the subjects with *NOTCH3* mutations exhibited more severe deep WMH, significantly higher scales of enlarged perivascular space in the basal ganglia, a higher number of lacunes in both lobar and deep brain regions, and increased CMBs, particularly in the thalamus, hippocampus, and insula.[35]

In summary, CADASIL patients with ICH exhibit more severe abnormalities in neuroimaging markers associated with CSVD, suggesting the presence of more fragile small cerebral vessels and an increased risk of ICH.

5. OUTCOME AND MANAGEMENT OF ICH IN CADASIL PATIENTS

The population-based Rotterdam study demonstrated that higher CSVD sum scores were associated with significantly increased risks of stroke, dementia, and mortality over a 10-year follow-up period.[65] Similarly, CADASIL patients who have ever experienced ICH show more severe CSVD-related MRI abnormalities compared with those without ICH, suggesting a poorer prognosis. In CADASIL patients harboring the *NOTCH3*

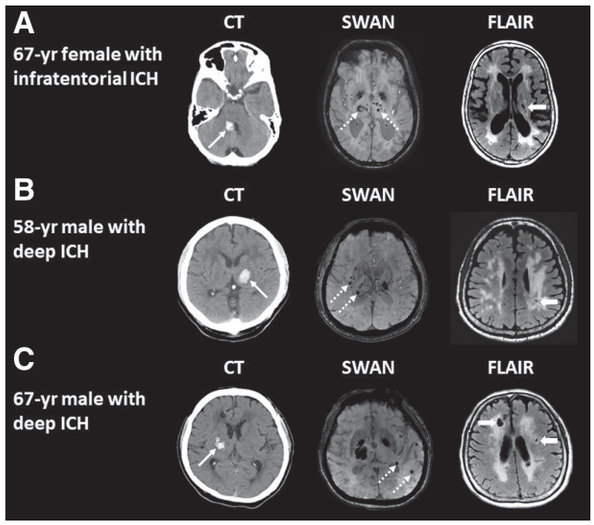

Fig. 2 Representative CT images and brain MRI, including SWI and T2-FLAIR, of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy who developed symptomatic ICH. A, A 67-y-old female with ICH in the right middle cerebellar peduncle (arrow), CMBs (dashed arrows), a lacune (arrowhead), and diffuse WMH. B, A 58-y-old male with ICH in the left thalamus (arrow), CMBs (dashed arrows), a lacune (arrowhead), and diffuse WMH. C, A 67-y-old male with ICH in the right internal capsule (arrow), CMBs (dashed arrows), lacunes (arrowheads), and diffuse WMH. CMBs = cerebral microbleeds; CT = computed tomography; FLAIR = fluid-attenuated inversion recovery; ICH = intracerebral hemorrhage; MRI = magnetic resonance imaging; SWI = susceptibility-weighted imaging; WMH = white matter hyperintensity.

p.R544C mutation, a study reported an annual stroke recurrence rate of 8.1 per 100 person-years, with a median follow-up of 66 months.[11] The recurrent rate was notably higher in patients with ICH as the initial stroke type compared with those whose onset manifestation was ischemic stroke (10.9% vs 7%, with a hazard ratio of 2.17), even after adjusting for age, gender, and hypertension. Furthermore, the mortality rate in the ICH-onset group was higher than that of the ischemic stroke-onset group (28.6% vs 8.7%). A comparative study of 45 ICH patients with *NOTCH3* mutations and 109 patients with sporadic ICH found that, although clinical severity was not necessarily greater in the group with *NOTCH3* mutation group, their annual stroke recurrence rate, particularly ICH rate, was significantly higher than the sporadic ICH group (9.1% vs 4.5%) over a follow-up period of 3.6 ± 3.2 years.[35] These findings indicate that CADASIL patients with ICH face substantially increased risks of recurrent strokes and mortality compared with both sporadic ICH patients and CADASIL patients without ICH. In addition, the presence of mixed CMBs in both deep and lobar regions was associated with increased stroke recurrence rates in both CADASIL-ICH and sporadic ICH groups, underscoring the need for vigilant monitoring of this high-risk population.[35]

Currently, there are no specific guidelines or consensus on the management of CADASIL patients with ICH or those at risk of developing ICH. As a result, real-world strategies are largely based on extrapolations from studies of sporadic CSVD and general ICH populations. For example, the recommendations of BP control for ICH from the American Heart Association and American Stroke Association guidelines suggest reducing systolic BP to below 140 mmHg in the acute stage of stroke and maintaining long-term BP targets below 130/80 mmHg.[66] However, more aggressive targets of below 120/80 mmHg have been proposed for CADASIL patients,[12] given that intensive BP control has been shown to significantly reduce recurrence rates of both ischemic and hemorrhagic strokes in the general population.[67] Moreover, findings from the Prevention of Serious Adverse Events Following Angiography trial (PRESERVE) indicated that such intensive BP management did not reduce cerebral perfusion in individuals with CSVD.[68] In CADASIL, continuous BP monitoring has demonstrated that elevated diastolic BP is particularly associated with an increased risk of stroke and worsening neuroimaging abnormalities, highlighting the need for strict control of diastolic BP.[69]

Regarding antithrombotic therapy, current evidence does not support the routine use of antiplatelet agents in CADASIL patients, particularly in those without a history of ischemic stroke.[70] In CADASIL patients with multiple CMBs, antiplatelet agents should be prescribed with caution due to the increased risk of ICH.[60,71] Furthermore, guidelines from the European Academy of Neurology advise against thrombolysis in CADASIL patients with acute ischemic stroke of small vessel etiology.[70] Nevertheless, a recent retrospective multicenter study in East Asia reported 12 CADASIL patients who received intravenous thrombolysis for acute ischemic stroke, finding it to be safe, with 83% of the patients achieving excellent functional outcomes (modified Rankin Scale score of 0 or 1) at 90 days poststroke.[72] Long-term anticoagulant therapy is generally not recommended for stroke prevention in CADASIL patients due to the heightened ICH risk; however, it should still be considered in cases with strong indications, such as atrial fibrillation or pulmonary embolism.[70]

Overall, the management of CADASIL patients with ICH largely relies on evidence extrapolated from broader studies on sporadic CSVD and general ICH populations. Dedicated research focusing on CADASIL-specific management strategies is urgently needed to guide clinical practice and improve patient outcomes.

In conclusion, this review provides focused insights into ICH in CADASIL, highlighting considerable variability in ICH prevalence influenced by ethnic factors and specific *NOTCH3* mutations, such as p.R544C and p.R75P. Key risk factors for ICH in CADASIL include hypertension and the presence of CMBs. ICH in CADASIL often presents as deep hemorrhages in the thalamus or basal ganglia and sometimes manifests with silent lobar hemorrhage. CADASIL patients with ICH lesions are associated with more severe neuroimaging abnormalities, including extensive WMH, multiple lacunes, and CMBs. Management strategies should emphasize strict BP control. Clinicians should exercise caution when prescribing antiplatelet agents in patients with a high burden of CMBs, while anticoagulant therapy should be reserved for those having strong indications to minimize the risk of ICH. Future studies are needed to explore the underlying causes of ethnic differences in ICH prevalence, the impact of specific genotypes, and potential preventive strategies for CADASIL patients.

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