BRIEF COMMUNICATION

CADASIL: two new cases with intracerebral hemorrhage

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Abstract

Whether cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a risk factor for spontaneous intracerebral hemorrhage (ICH) and influences outcomes remains unclear. In this study, we report two cases of CADASIL presenting with cerebral hemorrhages. These cases suggest that a CADASIL vasculopathy by itself mainly results in ICH, as indicated by slight vascular risk factors and prominent neuroimaging abnormalities, suggesting that CADASIL should be considered a risk factor for ICH. Interestingly, decreased perihematomal edema was noted in ICH patients with CADASIL in this study.

Introduction

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebral small-vessel disease (SVD) caused by a mutation in the Notch3 gene that leads to the accumulation of granular osmiophilic material (GOM) in arteries and the disintegration of vascular walls. Neuroimaging abnormalities such as cerebral white matter lesions (WMLs), lacunes, and microbleeds in the CADASIL patients are related to this cerebral small-vessel histopathology.1 While CADASIL is considered a primarily ischemic form of vascular dementia, spontaneous intracerebral hemorrhage (ICH) has recently been reported in association with CADASIL,2–6 suggesting that the structural fragility of arterial walls may lead to ICH attacks. However, there are limited data describing the effects that the underlying structural changes related to CADASIL have on the occurrence of ICH and subsequent outcomes.

In this study, we report on two unrelated CADASIL patients presenting with recurrent cerebral lobar hemorrhage and thalamic hemorrhage to determine the relationship between imaging manifestations of CADASIL and the occurrence and dynamic evolution of ICH. We also briefly review the literature on this issue.

Subjects

Case 1

A 65-year-old Chinese female was referred to our hospital because of memory decline for 3 years and limb weakness for 4 months. At the age of 62, she suffered a cerebral infarction, resulting in memory decline. At the age of 65, she had an ICH in the left thalamus, with an initial blood
pressure (BP) of 130/80 mmHg and presenting with limb weakness and worsened memory. Her personal medical history showed no other problems, and no drug treatments were given before or after ICH. Her family history showed that her father had three episodes of stroke and died at the age of 72. Her sister experienced severe cognitive decline after suffering a cerebral hemorrhage at the age of 60. Brain MRI revealed a hemorrhage in the left thalamus, confluent white matter hyperintensity in bilateral periventricular areas, some lacunes in basal ganglia and numerous microbleeds in the bilateral thalamus, basal ganglia, temporal lobe, frontal lobe, midbrain, and

**Figure 1.** Spontaneous cerebral hemorrhage in two patients with CADASIL. (A) Patient 1 carried the Arg544Cys NOTCH3 gene mutation and showed multiple white matter lesions, lacunar infarcts, numerous microbleeds (MB), and a cerebral hemorrhage (CH) lesion in the left thalamus on brain MRI. Two episodes of high blood pressure (11:00 to 11:30 and 17:30 to 18:00) were found using an ambulatory blood pressure monitor. (B) Brain images show three symptomatic CH lesions (CH1, CH2, CH3) and one asymptomatic cerebral hemorrhage (AsCH) in the left occipital lobe of patient 2, who carried the CGCT insertion in the NOTCH3 gene; multiple white matter lesions, lacunar infarcts and microbleeds were also shown by MRI. A skin biopsy showed deposits of granular osmiophilic material in the basement membranes of smooth muscle cells. In addition, an ambulatory blood pressure monitor revealed nocturnal hypertension and occasional daytime hypertension.
cerebellum (Fig. 1A). Notch3 gene testing revealed a heterozygous c.1630C > T mutation in exon 11, which leads to an arginine-to-cysteine substitution (p.Arg544Cys), consistent with the diagnosis of CADASIL.

The cause of her ICH was then investigated. On clinical examination, her BP was 129/84 mmHg (obtained using a mercury sphygmomanometer 4 months after ICH). However, an ambulatory BP monitor detected two episodes of high BP from 11:00 to 11:30 and 17:30 to 18:00. Her 24-hour systolic pressure was between 150 and 75 mmHg, and her diastolic pressure was between 62 and 97 mmHg (Fig. 1A). The diagnosis of hypertension was confirmed, and an antihypertensive treatment was administered to this patient.

**Case 2**

A 56-year-old Chinese man was admitted to our hospital for recurrent cerebral hemorrhage. Ten years ago, he suffered from his first cerebral hemorrhage in the right parietal lobe, with an initial BP of 135/70 mmHg. A month and a half ago, the patient experienced a second cerebral hemorrhage and was admitted to our hospital with an initial BP of 140/80 mmHg. He complained of sudden visual field defects and cognitive dysfunction. Brain imaging showed a cerebral hemorrhage in the left parietal lobe. In the third episode of cerebral hemorrhage (45 days after the second ICH), the patient presented with the acute onset of sensory aphasia with an acute cerebral hemorrhage in the left temporal lobe. When he was admitted to

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**Figure 2.** Evolution of hemorrhage and perihematomal edema in CADASIL and hypertension patients (HT). Minimal perihematomal edemas (yellow arrow) were noted in the cerebral hemorrhage associated with CADASIL (A, B) compared with the cerebral hemorrhage only associated with hypertension (C) at 1–3 days, 7 days and 14 days. Hemorrhage volume (red line) gradually decreased in both patients and showed no significant difference.
### Table 1. CADASIL cases with intracerebral hemorrhage.

| Author, year of publication | Sex/Age | WML | Lacune | Asymptomatic hemorrhage | BP | Cigarette | Alcohol | Antithrombotics | ICH site | HV | IV | HE | PHE | Any mass effect | Death |
|-----------------------------|---------|-----|--------|-------------------------|----|-----------|---------|---------------|----------|-----|----|-----|-----|----------------|-------|
| Maclean3                     | M/56    | 4   | yes    | 1 0                     | no | no        | yes     | no            | lobar    | small | no | no  | minimal | no | yes          |
| Ragoschke11                  | F/47    | 3   | yes    | 25 0                    | no | yes       | 100/63  | no            | cerebellum | small | no | no  | minimal | no | no          |
| Choi4                        | F/68    | 3   | yes    | 27 1                    | yes| yes       | NA      | no            | deep    | small | no | NA | NA | no | no          |
| M/69                        | 3       | yes | 85 0   | no                      | yes| NA        | no      | yes           | deep    | small | no | NA | NA | no | no          |
| M/61                        | 2       | yes | 14 0   | no                      | yes| NA        | no      | no            | deep    | small | no | NA | NA | no | no          |
| M/48                        | 2       | Yes | 5 0    | no                      | yes| NA        | no      | no            | deep    | small | no | NA | NA | no | no          |
| M/86                        | 3       | yes | 32 0   | no                      | yes| NA        | no      | no            | deep    | small | no | NA | NA | no | no          |
| Maclean12                   | M/45    | 3   | yes    | 6 0                     | no | yes       | 140/80  | no            | warfarin | deep | yes | no | significant | yes | no          |
| Oh13                        | M/39    | 2   | yes    | some 1                  | no | yes       | 140/90  | yes           | asprin  | lobar | large | no | no  | significant | no   |
| Lee14                       | M/43    | NA  | NA     | NA NA                   | no | yes       | 140/90  | yes           | asprin  | deep  | small | NA | NA | no | no          |
| M/57                        | 4       | yes | NA     | 0                       | no | yes       | NA      | no            | asprin  | lobar | deep | small | NA | NA | no          |
| M/56                        | NA      | NA  | NA     | NA NA                   | no | yes       | NA      | no            | asprin  | deep  | small | no | NA | NA | no          |
| Sano15                      | M/46    | 4   | yes    | NA 0                    | no | no        | NA      | yes           | ticlopidine | deep | large | no | no  | minimal | yes | no          |
| Pradotto10                  | M/55    | 4   | yes    | 3 0                     | no | no        | NA      | no            | heparin  | lobar | small | NA | minimal | no | no          |
| Delgado16                   | M/55    | 3   | yes    | NA NA                   | no | no        | NA      | no            | deep    | large | no | NA | minimal | no | no          |
| Lian9                       | M/46    | 4   | yes    | some NA                 | no | no        | 138/98  | yes           | deep    | large | yes | no | minimal | yes | no          |
| Rinnoci5                    | M/58    | 4   | yes    | 25 NA                   | no | yes       | 180/120 | no            | cerebellum | small | no | no  | minimal | no | no          |
| F/67                        | 4       | Yes | 2 NA   | no                      | yes| 190/110   | yes     | no            | lobar    | large | no | no  | minimal | no | no          |
| M/77                        | 4       | yes | 5 NA   | no                      | yes| NA        | no      | no            | deep    | small | no | NA | minimal | no | no          |
| Liao6                       | 55      | NA  | yes    | NA NA                   | NA | NA        | NA      | NA            | deep    | small | no | NA | minimal | NA | NA          |
| This study                  | M/56    | 3   | yes    | 22 1                    | no | yes       | 130/80  | yes           | lobar    | small | no | no  | minimal | no | no          |
| F/65                        | 2       | yes | 14 NA  | no                      | yes| 138/83    | no      | no            | lobar    | small | no | no  | minimal | no | no          |

WML, white matter lesion; MB, microbleed; DM, diabetes mellitus; HT, hypertension; BP, blood pressure; NA, not available; M, male; F, female; HV, hematoma volume; IV, intraventricular extension; HE, hematoma enlargement; PHE, perihematomal edema.

1WML grade was assigned using the scale described by van Sweiten.17
2BP on initial ICH.
3Diameter less than 50 mm.
4Diameter more than 50 mm.
5Location of deep hematoma includes basal ganglia or thalamus.
our stroke unit, his initial BP was 138/83 mmHg. His medical history included hypertension and nicotine and alcohol dependence. The patient had hypertension for fourteen years; captopril was taken at a dose of 12.5 mg every day, and his BP remained normotensive. No antithrombotic drugs were taken. His mother died of cerebral hemorrhage at 70 years old. Brain MRI of this patient was done on the 7th day of the third cerebral hemorrhage, showing diffuse WMLs in the periventricular region on T2 images and cerebral hemorrhaging in different lobar areas on T2* images. The patient also had lacunes in the bilateral thalamus and centrum semiovale and multiple microbleeds in the cerebellum, bilateral thalamus, temporal lobes, occipital lobes, and parietal lobes (Fig. 1B). A skin biopsy of the patient was performed, and deposits of GOM were identified in the basement membranes of smooth muscle cells (Fig. 1B). A NOTCH3 gene mutation analysis showed a CGCT insertion between nucleotides 2041 and 2042 of exon 13 (c.2041_2042insCGCT), which encodes EGFR17, resulting in an amino acid frameshift (cysteine to frameshift) at codon 681. A diagnosis of CADASIL was established.

The cause of recurrent ICH was then investigated. Ambulatory BP monitoring (8 days after the third ICH) revealed a 24- hour systolic pressure between 163 and 103 mmHg and a diastolic pressure between 112 and 63 mmHg. The rhythm showed a nondipping pattern and nocturnal hypertension, when BP occasionally increased above the daytime average (Fig. 1B).

To determine the dynamic evolution of ICH in CADASIL, the second and third ICH images from this patient were monitored at different time points. As shown in Figure 2A–B, there was no significant hematoma progression during the first day after ICH, and no intraventricular extension occurred. Edema volume expanded rapidly in the first 7 days, and expansion continued for up to 14 days in ICH patients caused only by hypertension (Fig. 2C). In contrast, in the CADASIL, edema volume expansion was much slower in the first 7 days and remained at a minimal level during the ensuing 8–21 days. ICH volumes gradually decreased over the next 14–21 days in both patients, with no significant difference between them (Fig. 2).

**Discussion and Conclusion**

At present, it is unclear whether ICH in the CADASIL patients develops as a part of the disease process associated with a specific genotype, as a result of the concurrent hypertension or occurs as a result of the use of antithrombotics. Although these two patients had mild hypertension, it may not have been the main cause of ICH because these patients did not show elevated BPs at the onset of ICH. So, our cases suggest that the CADASIL vasculopathy by itself mainly resulted in ICH, as indicated by slight vascular risk factors and prominent neuroimaging abnormalities (Grade 2 or 3 WMLs, more than 10 lacunes and microbleeds).

Published cases of CADASIL patients with ICH are reviewed in Table 1; including 17 men and six women, with a mean age of 56.5 years. Hypertension was present in 18 patients (78%), and one patient had diabetes mellitus. The average BP at the initial ICH was 150/93 mmHg. Other risk factors were heavy alcohol consumption in five patients (20%), smoking in 6 (26%), and the use of antithrombotic drugs in 7 (23%). The vascular risk factors in the CADASIL patients are slighter to those in primary spontaneous ICH patients. However, key imaging markers of cerebral SVD abnormalities were more severe in the CADASIL patients with ICH; 84% of these patients had grade 3–4 WMLs, and 100% showed numerous lacunes and microbleeds (Table 1). This evidence supports the idea that patients with CADASIL potentially have fragile small cerebral vessels and an increased susceptibility to hemorrhagic brain insult, and CADASIL should be considered a risk factor for ICH incidence.

In our cases, we also found that there was only a minimal and slow progression of perihematomal edema. This conclusion is supported by the data in Table 1. Twenty-eight percent of the ICHs were located in the lobes, 60% in the deep regions (basal ganglia or thalamus), and 12% in the cerebellum, and 24% of the ICHs were more than 5 cm wide at their largest diameter. No patients had hematoma enlargements, 8% of the patients showed intraventricular extension, and 8% of the patients showed significant perihematomal edema (Table 1). Histopathologic studies demonstrate a loss of structure in the arteriolar walls, narrowing of vessel lumens, and thickening of the vessel walls in patients with CADASIL. These changes may reductions blood perfusion of brain structures and restrict vasogenic edema, which contributed to minimal perihematomal edema in CADASIL.

In conclusion, this report demonstrates temporal characteristics of ICH in association with CADASIL, which suggests that ICH in patients with CADASIL is significantly different from primary cerebral hemorrhage, and specific management strategies for ICH patients with CADASIL are recommended.

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**Author Contribution**

ZQZ and YLW formulated the study concept; ZQZ acquired funding for the study; STN, XGW, HFT, XYY, BC, YZS, QHC, LYG, and YZP collected the data; CZ, LW and SWL analyzed the data; and CZ and ZQZ wrote the article.

**Conflict of Interest**

None.

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