APOE and Cerebral Small Vessel Disease Markers in Patients With Intracerebral Hemorrhage

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Neurology® 2022;99:e1290-e1298. doi:10.1212/WNL.0000000000200851

Abstract

Background and Objective

We investigated the associations between the APOE genotype, intracerebral hemorrhage (ICH), and neuroimaging markers of cerebral amyloid angiopathy (CAA).

Methods

We included patients from a prospective, multicenter UK observational cohort study of patients with ICH and representative UK population controls. First, we assessed the association of the APOE genotype with ICH (compared with controls without ICH). Second, among patients with ICH, we assessed the association of APOE status with the hematoma location (lobar or deep) and brain CT markers of CAA (finger-like projections [FLP] and subarachnoid extension [SAE]).

Results

We included 907 patients with ICH and 2,636 controls. The mean age was 73.2 (12.4 SD) years for ICH cases vs 69.6 (0.2 SD) for population controls; 50.3% of cases and 42.1% of controls were female. Compared with controls, any APOE e2 allele was associated with all ICH (lobar and nonlobar) and lobar ICH on its own in the dominant model (OR 1.38, 95% CI 1.13–1.7, p = 0.002 and OR 1.50, 95% CI 1.1–2.04, p = 0.01, respectively) but not deep ICH in an age-adjusted analyses (OR 1.26, 95% CI 0.97–1.63, p = 0.08). In the cases-only analysis, the APOE e4 allele was associated with lobar compared with deep ICH in an age-adjusted analyses (OR 1.56, 95% CI 1.1–2.2, p = 0.01). When assessing CAA markers, APOE alleles were independently associated with FLP (e4: OR 1.74, 95% CI 1.04–2.93, p = 0.04 and e2/e4: 2.56, 95% CI 0.99–6.61, p = 0.05). We did not find an association between APOE alleles and SAE.

Discussion

We confirmed associations between APOE alleles and ICH including lobar ICH. Our analysis shows selective associations between APOE e2 and e4 alleles with FLP, a CT marker of CAA. Our findings suggest that different APOE alleles might have diverging influences on individual neuroimaging biomarkers of CAA-associated ICH.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
Nontraumatic intracerebral hemorrhage (ICH) accounts for 10%–15% of all strokes in Western countries such as the United Kingdom and United States (but a high proportion in Asian countries), with a mortality of 40% at 1 month and 55% at 1 year.\(^1\)–\(^4\) Survivors frequently remain severely disabled.\(^5,6\) Moreover, the incidence of ICH in the elderly population seems to be increasing, possibly because of the increased use of oral anticoagulation.\(^5,8\) In over 80% of cases, nontraumatic ICH results from bleeding into the brain parenchyma from a small arteriole affected by cerebral small vessel diseases (SVDs). The commonest sporadic SVDs causing ICH are deep perforator arteriopathy (also termed hypertensive arteriopathy or arteriolosclerosis) and cerebral amyloid angiopathy (CAA). Deep perforator arteriopathy is associated with hypertension and is a frequent cause of deep ICH in the basal ganglia or brainstem; CAA is caused by \(\beta\)-amyloid deposition in cortical and leptomeningeal blood vessels and contributes to lobar ICH.\(^8\) CT scans can detect brain imaging biomarkers of SVD including white matter changes, lacunes, and atrophy (associated with both hypertensive arteriopathy and CAA) and, in the acute phase, ICH morphological features including finger-like projections (FLP) and subarachnoid extension (SAE), which are associated with CAA.\(^9,10\)

APOE has emerged as a strong genetic risk factor for ICH and its clinical consequences, possibly mediated by its role in membrane maintenance, neuronal repair, regulation, vascular integrity, and synaptic remodeling.\(^11\)–\(^13\) The APOE genotype is the combination of 2 variants (rs7412 and rs429358), which form combinations of the \(\varepsilon2\), \(\varepsilon3\), and \(\varepsilon4\) alleles. The most consistent and robust association is between APOE \(\varepsilon4\) and CAA, with or without ICH, although APOE \(\varepsilon2\) has been linked to ICH severity, perhaps because of increased vascular fragility.\(^14,15\) Studies in non-ICH populations suggest that APOE alleles can influence neuroimaging biomarkers of cerebral SVD.\(^16\)–\(^21\)

Despite these established associations between APOE alleles and ICH, we are not aware of any systematic studies in ICH linking them with neuroimaging markers of the underlying SVD type and severity.\(^16\)–\(^21\) We therefore systematically investigated the associations of APOE with the following: ICH presence and location, and neuroimaging (CT) biomarkers of the underlying arteriopathy type and severity. We hypothesized that APOE \(\varepsilon2\) and \(\varepsilon4\) alleles are associated with neuroimaging biomarkers of CAA seen on acute CT scans.

Glossary

CAA = cerebral amyloid angiopathy; CROMIS-2 = Clinical Relevance of Microbleeds in Stroke; cSS = cortical superficial siderosis; FLP = finger-like projections; ICH = intracerebral hemorrhage; MRC NSHD = Medical Research Council National Survey of Health and Development; SAE = subarachnoid extension; SVD = small vessel disease.

Methods

Study Design and Population

We included patients with ICH from the prospective multicenter Clinical Relevance of Microbleeds in Stroke (CROMIS-2) study (NCT02513316)\(^22\) ICH cohort. The full study protocol and baseline clinical data collection in CROMIS-2 are published elsewhere.\(^22\) For this analysis, we included patients who had imaging-confirmed ICH, a blood sample available for genetic analysis, and baseline neuroimaging (acute CT) available for central neuroimaging analysis. The population controls were recruited from the Medical Research Council National Survey of Health and Development (MRC NSHD, 1946 British birth cohort).\(^3\) The NSHD is based on a social class stratified sample (\(n = 5,362\)) of all singleton births in 1 week in March 1946 in England, Scotland, and Wales, broadly representative of the general population, and followed up to 24 times since birth. The study is uniquely placed to investigate life course factors associated with aging.\(^23\)

We collected detailed baseline characteristics and clinical presentation of patients with ICH using a standardized report questionnaire and definition of variables. NSHD data were collected by trained research nurses using standardized questionnaires.\(^10\) We included the following variables from both populations: age, sex, hypertension, diabetes mellitus, oral anticoagulation (defined as regular intake of any anticoagulation), antiplatelet medication (defined as regular intake of any antiplatelet medication), statins medication, antihypertensive medication, and smoker status.

Genotyping

The APOE genotype was determined using peripheral blood samples as follows. For CROMIS-2 patients, genomic DNA extraction was performed by the laboratory staff of the neurogenetics laboratory at the National Hospital of Neurology and Neurosurgery. APOE genotyping was performed as previously described.\(^24\) The person genotyping the samples (I.C.H.) was blinded to the clinical and neuroimaging data at the time of genotyping. See eTable 1, links.lww.com/WNL/C187, in the Supplement for primer sequence and reaction mix. The call rate was 94.9%. All samples were processed simultaneously to avoid batch effect. For the NSHD cohort, genotyping of the 2 single nucleotide variations (formerly SNPs), rs7412 and rs429358, used to determine the APOE genotype was performed at the LGC Genomics Limited (Hertfordshire, UK) using KASP assay technology.\(^25,26\)
We classified the different APOE genotype alleles as prespecified into present or absent (dominant model), allele count (additive model) to evaluate a linear change and looked at $\varepsilon 2/\varepsilon 4$ heterozygosity as a post hoc analysis.15,27 See Figure 1 for the flowchart of patient inclusion for this study. We genotyped 965 individuals of the CROMIS-2 study and included 2,636 population controls with an available APOE genotype. We included the 53 patients with cerebellar ICH location in the overall analysis but excluded them from the analysis of the lobar and deep categories.

**Neuroimaging Analysis**

All routine neuroimaging (CT) of patients in CROMIS-2 was coded, collected, and centrally stored at the Stroke Research Centre UCL Queen Square Institute of Neurology. Neuroimaging analysis was performed by clinical research fellows (D.W., I.C.H., G.B., and D.S.), all of whom were trained in neuroimaging rating and blinded to patient details. To evaluate raters’ accuracy, all raters independently rated a random sample of 50 CT scans. Hematoma location was defined as lobar or deep (with locations in the thalamus, basal ganglia, internal capsule, or brainstem but excluding cerebellar location) using a validated anatomic rating instrument (CHARTS).28 We excluded patients with multiple simultaneous ICH or cerebellar ICH (n = 53) from the ICH location subanalyses.29

On acute noncontrast CT scans, we evaluated the presence vs absence of SAE (i.e., acute blood in the extra-axial space) and FLP (elongated extensions, which arise from the hematoma, are longer than wide, and can extend to the cortex but do not have to), as markers of CAA, using published criteria and using standardized training available online30 (see Figure 2 for an example of SAE and FLP, respectively).31,32

**Statistical Analysis**

We followed a predefined analysis plan completed in January 2018. We first analyzed the association of APOE between individuals with ICH (cases) with individuals free of ICH (controls) using univariable and multivariable (adjusting only for age as a continuous variable) logistic regression models. In the second stage, we analyzed APOE and its association with neuroimaging features in patients with ICH. We used univariable and again age-adjusted multivariable regression models to assess the association between APOE and hematoma location (deep vs lobar) and neuroimaging markers of CAA, i.e., SAE and FLP.

We present categorical variables using frequency and percentages and continuous variables using mean ± SD. We investigated continuous variables for normal distribution. We compared categorical variables using the $\chi^2$ or Fisher exact test and continuous variables using the $t$ test or Mann-Whitney rank-sum as appropriate. The level of significance was set at 5% ($p = 0.05$). We performed all statistical analysis (ICH) in STATA 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

**Standard Protocol Approvals, Registrations, and Patient Consents**

The CROMIS-2 study was approved by the National Research Ethics Service (reference: 10/H0716/64, clinical trial registration on clinicaltrials.gov, NCT02513316). The MRC NSHD study was approved by the Central anchester Research Ethics Committee (reference: 07/H1008/168). Written informed consent...
was obtained from all patients or from the relative or representative where there was lack of capacity.

**Data Availability**

Anonymized data requests will be considered by the Steering Committee from any qualified investigator.

**Results**

**Population Summary**

Among the overall cohort of 1,094 patients with ICH, the APOE genotype was available in 907. The mean age was 73.2 years (SD 12.4 years), and 382 (42.1%) were female. The mean age of 2,636 controls (all with the APOE genotype available) was 69.5 years (SD 0.24), and 1,326 (50.3%) were female. See Table 1 for baseline characteristics and APOE genotype frequency according to the case-control status and ICH subgroup. Controls tended to be younger, more frequently female, and less frequently had hypertension and diabetes mellitus. With regard to drug intake, controls had a less frequent intake of all compared medications (oral anticoagulation, antiplatelets, and statins). Of the 907 patients with ICH, 371 (43.4%) had lobar and 483 (56.6%) deep ICH location (excluding 53 patients with cerebellar ICH). There was no difference between patients with the genotype available and those not (data not shown).

| Variable                             | Controls (n = 2,636) | All ICH (n = 907) | Lobar ICH (n = 371) | Deep ICH (excluding cerebellar) (n = 483) |
|--------------------------------------|---------------------|------------------|---------------------|------------------------------------------|
| Age, mean (SD)                       | 69.6 (0.2)          | 73.2 (12.4)      | 75.4 (10.8)         | 71.6 (13.2)                              |
| Female sex, N (%)                    | 1,326 (50.3)        | 382 (42.1)       | 172 (46.4)          | 183 (37.9)                               |
| Hypertension, N (%)                  | 574/1,822 (31.5)    | 586/890 (65.8)   | 230/364 (63.2)      | 316/475 (66.5)                           |
| Diabetes mellitus, N (%)             | 182/1,940 (9.4)     | 162/900 (18)     | 69/367 (18.8)       | 83/480 (17.3)                            |
| Smoker, N (%)                        | 197/2,084 (9.5)     | 88/875 (10.1)    | 28/355 (7.9)        | 54/468 (11.5)                            |
| OAC, N (%)                           | 82/1,819 (4.5)      | 349/903 (38.7)   | 154/370 (41.6)      | 164/480 (34.2)                           |
| Antiplatelet drugs, N (%)            | 277/1,819 (15.2)    | 219/901 (24.3)   | 91/369 (24.7)       | 121/479 (25.3)                           |
| Statins, N (%)                       | 637/1,819 (35)      | 459/896 (51.2)   | 194/368 (52.7)      | 234/475 (49.3)                           |
| Family history of ICH                | 84/859 (9.8)        | 31/350 (8.9)     | 49/461 (10.6)       |                                          |
| Previous ICH                         | 30/887 (3.4)        | 15/359 (4.2)     | 12/476 (2.5)        |                                          |
| Previous ischemic stroke             | 116/890 (13)        | 43/361 (11.9)    | 64/477 (13.4)       |                                          |

**APOE allele frequencies according to neuroimaging biomarkers of CAA**

| APOE, N (%) | SAE (139/371) | FLP (89/371) |
|-------------|---------------|--------------|
| APOE e2      |               |              |
| Any allele  | 394 (15)      | 188 (20.7)   | 92 (24.8)  | 89 (18.4) | 37 (26.6) | 23 (25.8) |
| 1 allele     | 374 (14.2)    | 173 (19.1)   | 83 (22.4)  | 83 (17.2) | 32 (23.0) | 21 (23.6) |
| 2 alleles    | 20 (0.7)      | 15 (1.6)     | 9 (2.4)    | 6 (1.2)   | 5 (3.6)   | 2 (2.3)   |
| APOE e3      |               |              |
| Any allele  | 2,465 (93.5)  | 832 (91.7)   | 327 (88.1) | 457 (94.6) | 119 (85.6) | 77 (86.5) |
| 1 allele     | 945 (35.8)    | 336 (37)     | 144 (38.8) | 175 (36.2) | 51 (36.7) | 39 (43.8) |
| 2 alleles    | 1,520 (57.7)  | 496 (54.7)   | 183 (49.3) | 282 (58.4) | 68 (48.9) | 38 (42.7) |
| APOE e4      |               |              |
| Any allele  | 789 (29.9)    | 255 (28.1)   | 115 (31)   | 123 (25.5) | 43 (30.9) | 36 (40.5) |
| 1 allele     | 705 (26.7)    | 228 (25.1)   | 99 (26.7)  | 115 (23.8) | 37 (26.6) | 43 (38.2) |
| 2 alleles    | 84 (3.2)      | 27 (3)       | 16 (4.3)   | 8 (1.7)    | 6 (4.3)   | 2 (2.3)   |
| e2/e4        | 67 (2.5)      | 32 (3.5)     | 19 (5.1)   | 11 (2.3)   | 9 (6.5)   | 8 (9.0)   |

FLP = finger-like projections; ICH = intracerebral hemorrhage; OAC = oral anticoagulation; SAE = subarachnoid extension.
Compared with controls (n = 2,636), we found an independent statistically significant association of the APOE ε2 allele as a dominant variable with all ICH (n = 907, OR 1.38, 95% CI 1.13–1.7, p = 0.002) and lobar ICH (n = 371, OR 1.50, 95% CI 1.1–2.04, p = 0.01) in the age-adjusted multivariable analysis; this risk increased with increasing allele count (additive model; overall p value = 0.003; Table 2). We found a weak, nonsignificant association of APOE ε2 with deep ICH (n = 483, OR 1.26, 95% CI 0.97–1.63, p = 0.08). For APOE ε4, we found no association

| Table 2 Associations of APOE With ICH (All, Lobar, and Deep) |
|-------------------------------------------------------------|
|                                | Univariable |                        | Multivariable (age adjusted) |
|                                | OR (95% CI) | p Value                 | OR (95% CI)                  | p Value                 |
| APoE ε2 dominant               |             |                         |                             |                          |
| All ICH                        | 1.49 (1.23–1.8) | <0.001                  | 1.38 (1.13–1.7)            | 0.002                   |
| Lobar ICH                      | 1.88 (1.45–2.43) | <0.001                  | 1.50 (1.1–2.04)            | 0.01                    |
| Deep ICH                       | 1.29 (1–1.66) | 0.05                    | 1.26 (0.97–1.63)           | 0.08                    |
| APoE ε2 additive               |             |                         |                             |                          |
| All ICH                        |             |                         |                             |                          |
| 1 allele                       | 1.44 (1.18–1.76) | <0.001                  | 1.34 (1.09–1.65)           | 0.003                   |
| 2 alleles                      | 2.34 (1.19–4.59) |                        | 2.09 (1.02–4.28)           |                         |
| Lobar ICH                      |             |                         |                             |                          |
| 1 allele                       | 1.78 (1.36–2.33) | <0.001                  | 1.38 (1–1.91)              | 0.003                   |
| 2 alleles                      | 3.62 (1.63–8.02) |                        | 3.79 (1.57–9.15)           |                         |
| Deep ICH                       |             |                         |                             |                          |
| 1 allele                       | 1.26 (0.97–1.64) | 0.12                    | 1.25 (0.96–1.63)           | 0.2                     |
| 2 alleles                      | 1.71 (0.68–4.28) |                        | 1.44 (0.55–3.77)           |                         |
| APoE ε4 dominant               |             |                         |                             |                          |
| All ICH                        | 0.92 (0.77–1.08) | 0.3                     | 0.96 (0.81–1.14)           | 0.63                    |
| Lobar ICH                      | 1.05 (0.83–1.33) | 0.68                    | 1.09 (0.83–1.42)           | 0.55                    |
| Deep ICH                       | 0.80 (0.64–1) | 0.05                    | 0.84 (0.67–1.05)           | 0.12                    |
| APoE ε4 additive               |             |                         |                             |                          |
| All ICH                        |             |                         |                             |                          |
| 1 allele                       | 0.92 (0.77–1.09) | 0.59                    | 0.96 (0.8–1.14)            | 0.88                    |
| 2 alleles                      | 0.91 (0.58–1.42) |                        | 0.99 (0.63–1.56)           |                         |
| Lobar ICH                      |             |                         |                             |                          |
| 1 allele                       | 1.01 (0.79–1.3) | 0.52                    | 1.00 (0.75–1.34)           | 0.14                    |
| 2 alleles                      | 1.37 (0.79–2.38) |                        | 1.79 (1–3.19)              |                         |
| Deep ICH                       |             |                         |                             |                          |
| 1 allele                       | 0.84 (0.67–1.05) | 0.06                    | 0.88 (0.7–1.1)             | 0.12                    |
| 2 alleles                      | 0.49 (0.23–1.02) |                        | 0.51 (0.24–1.06)           |                         |
| APoE ε2/ε4                     |             |                         |                             |                          |
| All ICH                        | 1.40 (0.91–2.15) | 0.12                    | 1.33 (0.85–2.08)           | 0.21                    |
| Lobar ICH                      | 2.07 (1.23–3.49) | 0.006                   | 1.82 (0.97–3.38)           | 0.06                    |
| Deep ICH                       | 0.90 (0.47–1.71) | 0.74                    | 0.90 (0.47–1.73)           | 0.76                    |

ICH = intracerebral hemorrhage.
with all, lobar, or deep ICH location compared with controls (Table 2, all p value >0.05). There was also weak, nonsignificant evidence for an association of e2/e4 with lobar ICH location (OR 1.82, 95% CI 0.97–3.38, p = 0.06).

**APOE and Location of ICH (Cases-Only Analysis)**

In the multivariable age-adjusted analyses, the APOE e4 allele was associated with lobar ICH location compared with deep ICH location (OR 1.56, 95% CI 1.1–2.2, p = 0.01, Table 3), and the strength of association increased with increasing allele count (OR of 1.38 for 1 and 4.66 for 2 alleles [95% CI 0.97–1.99 and 1.75–12.39, respectively, overall p = 0.003]). In the multivariable age-adjusted analyses, APOE e2/e4 heterozygosity was associated with lobar ICH location (OR 2.26, 95% CI 1.05–4.83, p = 0.04).

**APOE and Neuroimaging Markers of CAA**

In patients with lobar ICH, APOE e4 was associated with FLP as a dominant (OR 1.74, 95% CI 1.04–2.93, p = 0.04) and an additive variable (overall p value = 0.03, Table 4). Heterozygosity for e2/e4 was also associated with FLP (OR 2.56, 95% CI 0.99–6.61, p = 0.05). None of the APOE genotypes were associated with SAE in patients with lobar ICH, neither in the univariable nor in the age-adjusted multivariable analysis (Table 4). We conducted a sensitivity analysis adjusting the multivariable analysis for ICH volume in addition to age, which did not significantly change our results (eTable 2, links.lww.com/WNL/C187).

**Discussion**

In this analysis of a large well-phenotyped ICH cohort, we found that the APOE alleles e2 and e4 were independently associated with lobar ICH, APOE e2 when compared with controls, and APOE e4 when compared within patients with ICH. Our main new observation is that APOE e4 and e2/e4 alleles are selectively associated with FLP but not SAE. Our findings suggest that different APOE alleles have diverging influences on individual neuroimaging biomarkers, and thus potentially with different pathophysiological processes, in acute CAA-associated ICH.

Our study confirms and extends findings from prior studies: we found APOE e2 and e2/e4 to be associated with all ICH (compared with population controls) and e4 and e2/e4 with lobar ICH location (compared with a deep ICH location). Previous association findings of the APOE genotype with lobar and deep ICH location have been inconsistent. For example, one study found an association between APOE e4 and deep ICH location, whereas another did not. There could be several reasons for inconsistent findings: even slight changes in classification of ICH location could change associations with the APOE genotype. In the CROMIS-2 study, all imaging data were collected and rated centrally using a validated rating instrument, but this is not always the case. In line with other studies, we excluded cerebellar ICH location when assessing the subgroups of lobar and deep ICH. However, this is not routinely done and might also explain some inconsistencies.

In recent years, neuroimaging markers have been developed for CT imaging additionally to MRI. The recently reported associations between FLP and SAE with pathologically verified CAA prompted us to investigate whether these new biomarkers are associated with different APOE genotypes in our ICH cohort. Our data show that different neuroimaging markers show different associations with the APOE genotype: e2/e4 heterozygosity was consistently associated with an increased likelihood of FLP in patients with lobar ICH, as was e4 (in both dominant and
These addi

Our study has strengths. We included a large prospective cohort with extensive phenotype data, including standardized assessment of neuroimaging characteristics associated with CAA and SVD presence and severity.

Our study also has limitations. CROMIS-2 has a bias toward ICH survivors as the patient, or a representative, had to consent for the patient to be included in the study. Therefore, the patients with most severe ICH could not be included into CROMIS-2. Independent large cohorts are needed to verify our findings. Finally, we did not have information on ethnicity in our population controls, and some variables of interest, such as hypertension and anticoagulation, had a high missingness rate. This precluded safe multiple imputation, and therefore, only very limited statements about frequency could be made about them. In addition, ethnicity for our patients with ICH was self-reported. Ethnicity should ideally be checked with multiple dimensional scaling analysis as reported, and genotyped ethnicity can diverge significantly.

We confirm previously reported association between APOE alleles and lobar ICH. In addition, we show a selective association between the APOE e2 and e4 alleles with a CT-based neuroimaging marker of CAA, namely FLP. This might indicate that not all APOE alleles have the same effect on neuroimaging biomarkers of CAA-associated ICH and underlying pathophysiological processes. However, these results need to be replicated in a larger external, independent cohorts.

**Study Funding**

This study was funded by the Stroke Association (CROMIS-2) and the British Heart Foundation (grant TSA BHF 2009/01).
Disclosure
The authors report no relevant disclosures. Go to Neurology. org/N for full disclosures.

Publication History
Received by Neurology October 13, 2021. Accepted in final form April 28, 2022. Submitted and externally peer reviewed. The handling editor was José Merino, MD, MPhil, FAAN.

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