Family History of Stroke Is an Independent Risk Factor for Lacunar Stroke Subtype With Asymptomatic Lacunar Infarcts at Younger Ages

Iris L.H. Knottnerus, MD; Marij Gielen, MD, PhD; Jan Lodder, MD, PhD; Rob P.W. Rouhl, MD; Julie Staals, MD, PhD; Robert Vlietinck, MD, PhD; Robert J. van Oostenbrugge, MD, PhD

Background and Purpose—Results from case-control and case-case studies indicate that a positive family history of stroke (FHstroke) is an independent risk factor for lacunar stroke. Different lacunar stroke phenotypes can be distinguished on the basis of the presence of asymptomatic lacunar infarcts (aLACs), ischemic white-matter lesions, or brain microbleeds. The aim of the present study was to determine whether familial aggregation of stroke was different for lacunar stroke phenotypes.

Methods—In 157 patients with a first-ever lacunar stroke, a complete first-degree FHstroke was obtained by a standardized questionnaire and additional interview. Lacunar stroke patients were categorized successively into groups, depending on the presence of aLACs, ischemic white-matter lesions, and brain microbleeds on magnetic resonance imaging.

Results—Fifty-two percent of patients reported a positive FHstroke in at least one of their first-degree relatives. In younger (<65 years) probands, a high frequency of parental FHstroke (59% versus 20%, P<0.01) in those with aLACs compared with probands without aLACs was found. In multivariate analysis, the strongest associations were found for parental FHstroke (odds ratio=6.46; 95% CI=1.96 to 21.33), maternal FHstroke (odds ratio=4.00; 95% CI=1.18 to 13.56), and paternal FHstroke (odds ratio=5.40; 95% CI=1.14 to 25.61).

Conclusions—A family history of stroke might be an independent risk factor for the lacunar stroke phenotype with aLACs at younger ages, suggesting a role for genetic factors in this phenotype caused by diffuse vasculopathy. (Stroke. 2011; 42:00-00.)

Key Words: epidemiology ▪ family history ▪ genetics ▪ risk factors ▪ lacunar stroke

Lacunar stroke, which accounts for ~25% of all ischemic strokes, is defined as one of the lacunar syndromes with a compatible lacunar infarct on brain imaging.1 Lacunar infarcts are caused by occlusion of a single, small, perforating artery. Several pathology3 and clinical4,5 studies support the hypothesis that different subtypes of lacunar stroke exist: isolated lacunar infarct caused by a small, atheromatous plaque (microatheromatosis) and lacunar stroke with concomitant asymptomatic lacunar infarcts (aLACs) and/or diffuse white-matter lesions (WMIs) caused by diffuse vasculopathy of the cerebral small vessels, called lipohyalinosis. A third lipohyalinosis-associated lesion is the brain microbleed (BMB), which consists of the focal accumulation of hemosiderin-containing macrophages in the microvascular perivascular spaces.6,7

Family history studies support a role for genetic factors in the risk of stroke in general.8–10 Studies in which stroke was classified by subtype (for example, according to TOAST criteria) showed that a positive family history of stroke (FHstroke) was an independent risk factor for lacunar stroke, especially in younger patients.11–13 Because different pathologies underlie the subtypes of lacunar stroke, the influence of genetic factors in the development of lacunar stroke subtypes might be different. Therefore, familial aggregation of stroke could differ among the lacunar stroke subtypes, independent of conventional vascular risk factors, for example, hypertension and diabetes. The aim of the present study was to determine whether the familial aggregation of stroke was different for lacunar stroke subtypes. Therefore, we collected a FHstroke of first-degree relatives (FDRs) in a cohort of first-ever lacunar stroke patients who were subtype clinically and radiologically. We were especially interested in patients whose stroke occurred at younger ages (<65 years),
as we expected the largest role of genetic factors in that group.

Methods

Patients
As we employed a case-case study design, to avoid recall bias, we only included lacunar stroke patients. The consecutive registration of residential stroke patients at the Maastricht University Medical Centre (MUMC) has been described earlier. From this registry, lacunar stroke patients were included if they had a first-ever lacunar stroke, which was defined as (1) one of the recognized lacunar syndromes with a lesion on imaging compatible with the occlusion of a single, perforating artery or (2) when no such lesion was visible on imaging, established criteria of unilateral motor and/or sensory signs associated with lacunar stroke, which was defined as (1) one of the recognized lacunar syndromes with a lesion on imaging compatible with the occlusion of a single, perforating artery or (2) when no such lesion was visible on imaging, established criteria of unilateral motor and/or sensory signs that involved the whole of at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or cortical functions were used. Patients with lacunar stroke and a potential cardioembolic source of the embolus (for example, atrial fibrillation) and lacunar stroke patients with severe precerebral large-vessel disease (at least one internal carotid artery stenosis >50%) were excluded. Furthermore, when a monogenic cause of cerebral small-vessel disease (for example, CEDASIL) was considered, specific genetic tests were applied to confirm the diagnosis, and those patients were not included. By applying the same criteria, we also recruited 26 lacunar stroke patients from a nearby hospital (Orbis Medical Center, Sittard, The Netherlands) and 22 patients retrospectively from the earlier stroke registry at MUMC (February 1999 to September 2002). The final sample included 157 patients with a first-ever lacunar stroke. Clinical characteristics were documented at the time of stroke, as we expected the largest role of genetic factors in that group.

Obtaining FHstroke
A first-degree FHstroke was obtained by a written questionnaire given to the patient. During regular follow-up visits to the outpatient clinic, information was checked by the neurologist or resident by questioning the clinical picture in family members. When patients were unable to visit the outpatient clinic, information was verified by discussion with the patient or a close relative by telephone by the same investigator (I.L.H.K.). A positive FHstroke was defined as a history of stroke in at least one FDR. Nine different dichotomized categories of FHstroke were established: total (composite of all FDRs), female (mothers and sisters), male (fathers and brothers), parental (mothers and fathers), maternal, paternal, sibling (sisters and brothers), sister, and brother. Relatives’ medical records were unavailable to validate the subtype of stroke or vascular risk factor profile.

Imaging
Magnetic resonance images consisting of axial T2-weighted fast spin-echo, fluid-attenuated inversion-recovery and gradient echo sequences were obtained and assessed according to a previously described protocol. The symptomatic lacunar infarct, aLACs, and WMLs on the modified Fazekas scale were defined as described previously. BMBS were defined as punctuate, hypointense lesions on gradient echo images with a diameter of <10 mm. Two experienced vascular neurologists assessed the magnetic resonance imaging images by consensus. The interobserver agreement, expressed by Cohen’s κ, was determined before the study: 0.89 for symptomatic infarct, 0.96 for the presence of ≥1 aLACs, 0.77 for periventricular WMLs, 0.84 for deep WMLs, and 0.68 for BMBS.

Subtyping of Lacunar Stroke
Consecutively, each patient was evaluated for the presence of aLACs, WMLs, and BMBS. First, they were placed in the category of aLACs-positive when ≥1 aLACs was present and aLACs-negative when none were present. Second, all cases were reevaluated for the presence of extensive WMLs. Cases were categorized as WML-positive when the periventricular WML score on the modified Fazekas scale was 3 and/or the deep WML score was 2 or 3; otherwise, they were scored as WML-negative. Third, in 115 patients, gradient echo weighted images were available. When BMBS were present, those cases were classified as BMB-positive; otherwise, cases were classified as BMB-negative.

Statistical Analysis
Continuous data are presented as mean±SD and categorical variables as counts and frequencies. We compared means by the two-sample independent t test, because all continuous variables were normally distributed. Pearson’s χ² statistic or Fisher’s exact text was used for categorical variables.

Binary univariate and multivariate logistic-regression analyses were performed with lacunar stroke phenotype (that is, aLACs, WMLs, or BMBS) as the dependent variable and 1 of the 9 categories of FHstroke as the independent variable of interest. The following covariates were considered: age, sex, hypertension, diabetes mellitus, current or previous smoking habit, levels of cholesterol on admission, and coronary artery disease. Additionally, because data collection might influence the results, cohort (prospective MUMC, retrospective MUMC, and prospective Orbis Medical Center) was considered a covariate. Covariates were entered into the multivariate logistic-regression analysis in case of an association between the covariate and aLACs, WMLs, or BMBS. A probability value <0.1 was chosen as statistically significant only in this context. The selected covariates were forced into the multivariate model simultaneously (enter method in SPSS).

Because there is evidence suggesting that genetic factors are more important in younger individuals,13 we tested whether age was an effect modifier. Therefore, the interaction between FHstroke and a dichotomized age variable (at 65 years) was included in a multivariate logistic-regression model in which lacunar stroke phenotype was the dependent variable. The population was divided into 2 groups, younger (<65 years) and older (≥65 years) probands, and the relation between FHstroke and the different lacunar stroke phenotypes was evaluated as described. A two-tailed probability value <0.05 was considered statistically significant. Analyses were performed with the statistical software packages SPSS (version 16.0 for Windows, SPSS Inc, Chicago, IL).

Results

Clinical Characteristics
Clinical characteristics of younger (n=80) and older (n=77) probands for the different lacunar stroke phenotypes are depicted in Table 1 (and in Table 3 for older probands in the online-only Data Supplement, http://stroke.ahajournals.org). In 97 of 157 patients (62%), one or more aLACs were present. In young probands, differences were found in the prevalence of diabetes (18% for aLACs-positive versus 3% for aLACs-negative; P<0.01) and smoking (78% versus 56%, respectively; P<0.05). We found that 55 of 157 patients (35%) had extensive WMLs, as evaluated on the modified Fazekas scale. In young probands, male sex was less frequent in those with extensive WMLs (39% versus 66%, P<0.1). One or more BMBS were observed in 37 of 115 patients (32%). In younger probands, the BMBS-positive group had a smaller proportion of males (46% versus 77%, P<0.05), but more had coronary artery disease (23% versus 5%, P<0.1).

FHstroke
A FHstroke in any FDR was present in 81 of 157 patients (52%). In younger patients with aLACs, a parental (59% versus 20%, P<0.01) and maternal (42% versus 14%,
FHstroke was more frequent than in those without aLACs (Table 1). Because we did not find differences in sibling FHstroke, this higher number of affected parents caused the high prevalence of FDR FHstroke in patients with aLACs compared with those without aLACs (61% versus 37%, \(P<0.05\)). In patients older than 65 years, the frequency of an FHstroke was similar for those with or without aLACs (Supplemental Table 3). The prevalence of a FHstroke in probands with or without extensive WMLs was similar. In older probands with BMBs, a maternal FHstroke was more frequent than in probands without BMBs (38% versus 11%, \(P<0.05\)); however, the number of probands in those groups was very limited.

**Logistic-Regression Analysis**

In separate logistic-regression analysis to evaluate the age effect, the interaction between age and FHstroke was significant for aLACs (\(P=0.02\)) but not for WMLs or BMBs. In evaluating the association between lacunar stroke phenotype and FHstroke, the strongest associations were found in younger probands with aLACs for FDR FHstroke, parental FHstroke, maternal FHstroke, and paternal FHstroke, as shown in Table 2.

### Table 1. Clinical Characteristics and FHstroke in Younger Lacunar Stroke Patients (<65 Years, n=80) for Different Lacunar Stroke Phenotypes

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>aLACs-Negative (n=35)</th>
<th>aLACs-Positive (n=45)</th>
<th>Extensive WMLs</th>
<th>BMBs-Negative (n=39)</th>
<th>BMBs-Positive (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.6±6.8</td>
<td>52.7±7.0</td>
<td>52.9±6.8</td>
<td>54.1±7.3</td>
<td>54.8±6.6</td>
</tr>
<tr>
<td>Male</td>
<td>22 (63)</td>
<td>27 (60)</td>
<td>44 (66)</td>
<td>5 (39)*</td>
<td>30 (77)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (49)</td>
<td>28 (62)</td>
<td>37 (55)</td>
<td>8 (62)</td>
<td>24 (62)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (3)</td>
<td>8 (18)*</td>
<td>9 (11)</td>
<td>0</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.8±1.3</td>
<td>5.9±1.4</td>
<td>5.8±1.2</td>
<td>6.2±1.7</td>
<td>5.7±1.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (56)</td>
<td>35 (78)†</td>
<td>44 (67)</td>
<td>10 (77)</td>
<td>27 (69)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (9)</td>
<td>3 (7)</td>
<td>4 (6)</td>
<td>2 (15)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

FHstroke indicates family history of stroke; aLACs, asymptomatic lacunar infarcts; WMLs, white-matter lesions; BMBs, brain microbleeds; and FDRs, first-degree relatives. Data are presented as mean±SD or counts (%) in the clinical characteristics part of table and as counts (%) of probands with a positive FHstroke in that part of table.

*\(P<0.1\), †\(P<0.05\), ‡\(P<0.01\).

**Table 2. FHstroke in Relation to Lacunar Stroke Phenotypes for Younger Probands (<65 Years)**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Model OR (95% CI)</th>
<th>Multivariate Adjusted Model OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aLACs</td>
<td>WMLs</td>
</tr>
<tr>
<td>All FDRs</td>
<td>2.69 (1.08–6.72)*</td>
<td>1.17 (0.35–3.84)</td>
</tr>
<tr>
<td>Female</td>
<td>1.83 (0.71–4.69)</td>
<td>1.64 (0.49–5.45)</td>
</tr>
<tr>
<td>Male</td>
<td>3.10 (1.00–9.64)</td>
<td>2.13 (0.61–7.47)</td>
</tr>
<tr>
<td>Parents</td>
<td>5.65 (2.01–15.90)†</td>
<td>0.89 (0.26–3.03)</td>
</tr>
<tr>
<td>Mother</td>
<td>4.32 (1.40–13.29)*</td>
<td>1.63 (0.47–5.65)</td>
</tr>
<tr>
<td>Father</td>
<td>3.91 (0.99–15.40)</td>
<td>1.42 (0.33–6.02)</td>
</tr>
<tr>
<td>Siblings</td>
<td>0.61 (0.18–2.02)</td>
<td>1.65 (0.39–7.07)</td>
</tr>
<tr>
<td>Sister</td>
<td>0.42 (0.09–1.92)</td>
<td>1.79 (0.32–10.03)</td>
</tr>
<tr>
<td>Brother</td>
<td>1.03 (0.22–4.96)</td>
<td>2.18 (0.38–12.70)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; FHstroke, family history of stroke; aLACs, asymptomatic lacunar infarcts; WMLs, white-matter lesions; BMBs, brain microbleeds; and FDR, first-degree relative. Multivariate analyses were adjusted for age (continuous), diabetes, smoking, sex, and coronary artery disease.

*\(P<0.05\), †\(P<0.01\).*
in older probands, no association was found for aLACs and FDR FHstroke (univariate odds ratio [OR] = 0.85; 95% CI = 0.33 to 2.21; multivariate OR = 0.78; 95% CI = 0.26 to 2.31), parental FHstroke (univariate OR = 0.96; 95% CI = 0.35 to 2.37; multivariate OR = 0.93; 95% CI = 0.28 to 3.11), or sibling FHstroke (univariate OR = 0.80; 95% CI = 0.28 to 2.28; multivariate OR = 0.58; 95% CI = 0.16 to 2.03; Supplemental Table 4). Overall, parental and sibling FHstroke had no influence on the presence of WMLs or BMBs in univariate and multivariate analyses, irrespective of patient age (Table 2, and Supplemental Table 4 for older probands).

Discussion

By means of a case-case study design, we studied FHstroke in a substantial cohort of well-subtyped lacunar stroke patients. A parental history of stroke was an independent risk factor for patients with aLACs, which was confined to younger patients (<65 years).

Familial aggregation of stroke in lacunar stroke patients is suggestive of a genetic component. We found a significant association between positive parental FHstroke and the subtype with aLACs. Patients with concomitant aLACs more often have a diffuse arteriopathy of the small, penetrating arteries than do those without aLACs. Recent observations suggest that activation of the cerebral microvascular endothelium, followed by leakage of the blood-brain barrier, is causative in the development of this arteriopathy and subsequently of aLACs. There is limited evidence of endothelium-related polymorphisms, as the angiotensin-converting enzyme insertion/deletion polymorphism and the homocysteine-related, methylene tetrahydrofolate reductase-677 polymorphism are of influence in the subtypes of lacunar stroke with silent ischemic lesions. Our study supports a role for genetic factors in the lacunar stroke subtype with aLACs.

FHstroke is an independent risk factor for stroke at younger ages. In our study, we found that in younger patients, the familial aggregation of stroke was caused by a higher number of affected parents. This could be due to genetic factors, which could play a more prominent role at younger ages. However, because memory problems increase with age, this could also explain the difference, although it cannot explain the differences between the lacunar stroke subtypes (aLACs-positive versus aLACs-negative), as those patients were the same age.

A strength of our study is that we were able to collect a reasonable cohort of carefully subtyped lacunar stroke patients. Subtyping was conducted by combining established criteria of the classic lacunar syndromes with imaging criteria, and second by excluding patients with a possible embolic origin of the (lacunar) infarct, for example, atrial fibrillation and carotid artery disease. This enabled us to define a strict phenotype of the lacunar stroke patient who most probably developed the stroke owing to intrinsic disease of the cerebral small vessels. Our classification system was free of vascular risk factors, as suggested for studies on the pathophysiology of lacunar stroke. Furthermore, we used a case-case study model, as we aimed to compare different subtypes of lacunar stroke, thereby avoiding recall bias, which can undermine case-controls studies, as stroke patients are likely more aware of any FHstroke than are controls. In the total group of lacunar stroke patients, 52% reported to have at least one affected family member; this figure is in line with results from previous case-control studies, wherein a prevalence of FHstroke of 43% to 50% in lacunar stroke patients compared with a 30% prevalence in healthy controls was reported.

Familial clustering of risk factor profiles and lifestyle, such as diet and physical activity, could be alternative explanations for the familial aggregation of stroke in lacunar stroke patients. The familial clustering of vascular risk factors, for example, hypertension and diabetes, is almost always the case. In our study, the adjusted logistic-regression analyses for the aLACs phenotype yielded results similar to those of the unadjusted analyses.

Previous studies suggest that similar stroke subtypes do occur in family members, as monozygotic twins were more concordant for WMLs than were dizygotic twins. A high heritability of WMLs was found in family members of the Framingham cohort, and a high prevalence of microangiopathic lesions in siblings of lacunar stroke patients was reported. Therefore, one could speculate that the chance of lacunar stroke in FDRs of our patients is higher than the chance of another stroke subtype in those FDRs.

In this study, we found no association with the extent of WMLs. WMLs were evaluated on a visual rating scale, that is, the Fazekas scale. This scale correlates acceptably to quantitative lesion volumes; however, visual rating scales may show a so-called ceiling effect. Owing to this ceiling effect, we might have missed an association between the extent of WMLs and FHstroke.

The association of parental stroke with younger age and silent lacunar infarcts suggests the possibility of a direct, dominant genetic effect, as seen in CADASIL or Fabry disease. By extensive evaluation of each case before study inclusion and follow-up of patients by a team of vascular neurologists, we tried to exclude monogenic cases. However, as incomplete pictures of CADASIL and the phenotypic variance of heterozygous female carriers (Fabry disease) are known, we cannot completely exclude the inclusion of these patients.

In conclusion, we found that a parental FHstroke might be an independent risk factor for the subtype of lacunar stroke with concomitant aLACs, although confined to younger patients. This finding could suggest a role for genetic factors in the subtype of lacunar stroke caused by diffuse vasculopathy. Genes influencing endothelial function might play a role, as activation of the microvascular cerebral endothelium might be the initiating step in the development of aLACs. For future studies, stringent phenotyping is a prerequisite, as different genes and environmental factors might play different roles in the subtypes of lacunar stroke. Our findings require confirmation in other cohorts of well-subtyped lacunar stroke patients.

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Disclosures

None.

References

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SUPPLEMENTAL MATERIAL for the article “Family History of Stroke is an Independent Risk Factor for Lacunar Stroke Subtype with Asymptomatic Lacunar Infarcts at Younger Ages” by Iris LH Knottnerus et al.

This supplemental material comprises tables 3 and 4.

Table 3. Clinical characteristics and FHstroke in older lacunar stroke patients (≥65 years, n=77) for different lacunar stroke phenotypes

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Asymptomatic lacunar infarcts</th>
<th>Extensive white matter lesions</th>
<th>Brain Microbleeds (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aLACs - (n=25)</td>
<td>aLACs + (n=52)</td>
<td>WML - (n=35)</td>
</tr>
<tr>
<td>Age</td>
<td>71.6 ± 5.4</td>
<td>72.9 ± 5.8</td>
<td>72.8 ± 6.3</td>
</tr>
<tr>
<td>Male</td>
<td>10 (40)</td>
<td>32 (62)†</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (64)</td>
<td>36 (71)</td>
<td>25 (74)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3 (12)</td>
<td>9 (17)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.7 ± 1.1</td>
<td>5.6 ± 1.2</td>
<td>5.5 ± 1.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (30)</td>
<td>23 (46)</td>
<td>15 (46)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (4)</td>
<td>11 (21)†</td>
<td>4 (11)</td>
</tr>
<tr>
<td>FHstroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All first degree relatives</td>
<td>14 (56)</td>
<td>27 (52)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (20)</td>
<td>17 (32)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (44)</td>
<td>18 (35)</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Parents</td>
<td>10 (44)</td>
<td>20 (43)</td>
<td>18 (55)</td>
</tr>
<tr>
<td>Mother</td>
<td>4 (17)</td>
<td>11 (24)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Father</td>
<td>6 (25)</td>
<td>9 (19)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Siblings</td>
<td>8 (32)</td>
<td>14 (28)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Sister</td>
<td>2 (8)</td>
<td>8 (15)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Brother</td>
<td>7 (28)</td>
<td>12 (24)</td>
<td>10 (29)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or counts(%) in upper part of table and counts of probands(%) with a positive FHstroke in lower part of table. †P<0.1  *P<0.05  ‡P<0.01
Table 4. Family history of stroke in relation to lacunar stroke phenotypes for older probands (≥65 years).

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Model OR (95%CI)</th>
<th></th>
<th>Adjusted Model OR (95%CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic lacunar infarcts</td>
<td>White matter lesions</td>
<td>Brain microbleeds</td>
<td>Asymptomatic lacunar infarcts</td>
</tr>
<tr>
<td>All FDR</td>
<td>0.85 (0.33-2.21)</td>
<td>0.75 (0.30-1.85)</td>
<td>1.63 (0.59-4.56)</td>
<td>0.78 (0.26-2.31)</td>
</tr>
<tr>
<td>Female</td>
<td>1.94 (0.62-6.07)</td>
<td>0.60 (0.22-1.62)</td>
<td>2.77 (0.90-8.51)</td>
<td>1.16 (0.32-4.27)</td>
</tr>
<tr>
<td>Male</td>
<td>0.67 (0.25-1.79)</td>
<td>0.53 (0.21-1.35)</td>
<td>0.48 (0.16-1.47)</td>
<td>0.80 (0.27-2.40)</td>
</tr>
<tr>
<td>Parents</td>
<td>0.96 (0.35-2.37)</td>
<td>0.40 (0.15-1.06)</td>
<td>1.43 (0.48-4.24)</td>
<td>0.93 (0.28-3.11)</td>
</tr>
<tr>
<td>Mother</td>
<td>1.57 (0.44-5.59)</td>
<td>0.73 (0.23-2.29)</td>
<td>4.92 (1.26-19.23)*</td>
<td>1.11 (0.25-4.99)</td>
</tr>
<tr>
<td>Father</td>
<td>0.71 (0.22-2.30)</td>
<td>0.35 (0.11-1.16)</td>
<td>0.13 (0.07-1.45)</td>
<td>1.10 (0.28-4.33)</td>
</tr>
<tr>
<td>Siblings</td>
<td>0.80 (0.28-2.28)</td>
<td>0.80 (0.30-2.16)</td>
<td>0.65 (0.19-2.16)</td>
<td>0.58 (0.16-2.03)</td>
</tr>
<tr>
<td>Sister</td>
<td>2.09 (0.41-10.67)</td>
<td>0.51 (0.13-1.97)</td>
<td>0.62 (0.11-3.47)</td>
<td>1.32 (0.22-8.00)</td>
</tr>
<tr>
<td>Brother</td>
<td>0.79 (0.27-3.35)</td>
<td>0.70 (0.25-1.99)</td>
<td>0.56 (0.15-2.04)</td>
<td>0.60 (0.16-2.23)</td>
</tr>
</tbody>
</table>

Data are depicted as OR (95%CI). Multivariate analysis (#) were adjusted for age (continuous), diabetes, smoking, gender and coronary artery disease. *P<0.05
卒中家族史是年轻腔隙性卒中患者 aLACs 型的独立危险因素

Family History of Stroke Is an Independent Risk Factor for Lacunar Stroke Subtype With Asymptomatic Lacunar Infarcts at Younger Ages

Iris L.H. Knottnerus, MD; Marij Gielen, MD, PhD; Jan Lodder, MD, PhD; Rob P.W. Rouhl, MD; Julie Staals, MD, PhD; Robert Vlietinck, MD, PhD; Robert J. van Oostenbrugge, MD, PhD

背景和目的：病例对照研究和病例-病例研究的结果提示阳性卒中家族史 (FHstroke) 是腔隙性卒中的一个独立危险因素。不同腔隙性卒中亚型可分为无症状腔隙性梗死 (aLACs)、缺血性白质病变及脑微出血。该研究的目的是探讨不同类型腔隙性卒中家族聚集性是否不同。

方法：通过对 157 例腔隙性卒中患者进行标准问卷和附加的探访，得到了这些患者完整的一级亲属卒中史。按 MRI 表现将上述患者分为 3 组，即 aLACs 组、缺血性白质病变组及脑微出血组。

结果：52% 的患者至少一个一级亲属有卒中史。在年轻先证者 (<65 岁) 中，有 aLACs 者其父母有卒中史的比率比那些无 aLACs 者高 (59% vs 20%, P<0.01)。在多因素分析中，关联最强的因素为父母卒中史 (OR=6.46; 95% CI=1.96-21.33)、母亲卒中史 (OR=4.00; 95% CI=1.18-13.56) 和父亲卒中史 (OR=5.40; 95% CI=1.14-25.61)。

结论：卒中家族史可能是年轻腔隙性卒中患者 aLACs 亚型的独立危险因素，提示了遗传因素在这种由弥散的血管病变导致的卒中亚型中的作用。

关键词：流行病学, 家族史, 遗传, 危险因素, 腔隙性卒中

(Stroke. 2011;42:1196-1200. 郑州大学附属第一医院神经内科 李卓 王莉梅 译 许予明 校)
Family History in Lacunar Stroke

The clinical characteristics of patients with lacunar stroke are shown in Table 1 (longitudinal data are available in Online Supplement Table 3). The prevalence of risk factors, such as hypertension, diabetes, and smoking, is significantly higher in the young group compared to the elderly group. The analysis of the association between family history and lacunar stroke phenotype was performed using logistic regression analysis. The results showed that the young group had a higher prevalence of family history compared to the elderly group. The statistical significance was determined using a two-tailed test with a p-value of less than 0.05. The analysis was performed using SPSS statistical software (version 16.0; SPSS Inc, Chicago, IL).
表1 不同腔隙性卒中分型的年轻患者 (<65岁, n=80) 的临床特征和卒中家族史

<table>
<thead>
<tr>
<th></th>
<th>aLACs (n=35)</th>
<th>广泛WMLs (n=67)</th>
<th>BMBs (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄, 岁</td>
<td>53.6±6.8</td>
<td>52.9±6.8</td>
<td>54.8±6.6</td>
</tr>
<tr>
<td>男性</td>
<td>22 (63)</td>
<td>37 (55)</td>
<td>24 (62)</td>
</tr>
<tr>
<td>高血压</td>
<td>17 (49)</td>
<td>35 (52)</td>
<td>24 (46)</td>
</tr>
<tr>
<td>糖尿病</td>
<td>1 (3)</td>
<td>9 (11)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>总胆固醇 (mmol/L)</td>
<td>5.8±1.3</td>
<td>5.8±1.2</td>
<td>5.7±1.3</td>
</tr>
<tr>
<td>吸烟</td>
<td>19 (56)</td>
<td>44 (66)</td>
<td>24 (62)</td>
</tr>
<tr>
<td>冠状动脉疾病</td>
<td>3 (9)</td>
<td>9 (11)</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>

卒中家族史

<table>
<thead>
<tr>
<th></th>
<th>未调整的模型 OR(95% CI)</th>
<th>多元调整模型 OR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aLACs</td>
<td>WMLs</td>
<td>BMBs</td>
</tr>
<tr>
<td>一级亲属</td>
<td>2.69 (1.08–6.72)*</td>
<td>1.17 (0.35–3.84)</td>
</tr>
<tr>
<td>女性</td>
<td>1.83 (0.71–4.69)</td>
<td>1.64 (0.49–5.45)</td>
</tr>
<tr>
<td>男性</td>
<td>3.10 (1.00–9.64)</td>
<td>2.13 (0.61–7.47)</td>
</tr>
<tr>
<td>父亲</td>
<td>5.65 (2.01–15.90)*</td>
<td>0.89 (0.26–3.03)</td>
</tr>
<tr>
<td>母亲</td>
<td>4.32 (1.40–13.29)*</td>
<td>1.63 (0.47–5.65)</td>
</tr>
<tr>
<td>兄弟姐妹</td>
<td>3.91 (0.99–15.40)</td>
<td>1.42 (0.33–6.02)</td>
</tr>
</tbody>
</table>

OR, 比值比; CI, 置信区间; aLACs, 无症状的腔隙性脑梗死; WMLs, 脑白质病变; BMBs, 脑微出血; 多元分析因年龄(持续的)、饮食、吸烟、性别和冠状动脉疾病而作出相应的调整。

*P<0.05, †P<0.01.
无广泛 WMLs 的先证者中，卒中家族史的发生率相似。与无 BMBs 的年长先证者相比，有 BMBs 的年
长先证者母亲卒中更常见（分别为 38% 和 11%，P<0.05）；但是该组中先证者的数量有限。

Logistic 回归分析

应用单因素回归分析评估年龄的影响，年龄和家族卒中史的交互作用对 aLACs 型有统计学意
义（P=0.02），但对 WMLs 型或 BMBs 型无统计学意义。在评估腔隙性卒中亚型和家族卒中史的相
关系时，年轻腔隙性卒中患者一级亲属卒中史、双亲卒中史、母亲卒中史与 aLACs 型（如表 2 所示）相
关。未发现同胞卒中史与腔隙性卒中亚型相关。年老腔隙性卒中患者中，未发现一级亲属卒中
史（单变量 OR 值=0.85；95% CI=0.33-2.21；多变量 OR 值=0.78；95% CI=0.26-2.31）、父母卒中史
（单变量 OR 值=0.96；95% CI=0.35-2.37；多变量 OR 值=0.93；95% CI=0.28-3.11）与 aLACs 型无相关性，不论年龄（见表 2，年长先证者见补充表 4）。

讨论

通过病例-病例研究方法设计，我们研究了一群分型明确的腔隙性卒中患者的卒中家族史。父母
卒中史是 aLACs 型的独立危险因素，但仅限于较轻的患者（<65 岁）。

腔隙性卒中的家族性卒中聚集现象提示遗传性因素的作用。我们发现父母卒中家族史和 aLACs
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一样，完全排除这些患者。

总之，我们发现父母卒中史可能是腔隙性卒中aLACs型的独立危险因素，虽然只限于年轻患者。这项结果提示了遗传因素可能在弥漫性血管病变引起的腔隙性卒中中发挥作用。影响血管内皮的基因可能会起一定的作用，激活大脑微血管内皮可能是无症状性腔梗发展的启动步骤。在未来的研究中，严格的分型是一个必要条件，因为不同的基因和环境因素可能在不同的腔隙性卒中各亚型中扮演不同的角色。我们的研究结果也需要在其他分型明确的腔隙性卒中患者队列中进行确认。

参考文献