Recurrent hemorrhage risk and mortality in hereditary and sporadic cerebral amyloid angiopathy

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ABSTRACT

Objective: To determine whether hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), a monogenetic disease model for the sporadic variant of amyloid angiopathy (sCAA), has a comparable recurrent intracerebral hemorrhage (ICH) risk and mortality after a first symptomatic ICH.

Methods: We included patients with HCHWA-D from the Leiden University Medical Center and patients with sCAA from the Massachusetts General Hospital in a cohort study. Baseline characteristics, hemorrhage recurrence, and short- and long-term mortality were compared. Hazard ratios (HRs) adjusted for age and sex were calculated with Cox regression analyses.

Results: We included 58 patients with HCHWA-D and 316 patients with sCAA. Patients with HCHWA-D had fewer cardiovascular risk factors (≥ 1 risk factor 24% vs 70% in sCAA) and were younger at the time of presenting hemorrhage (mean age 54 vs 72 years in sCAA). Eight patients (14%) with HCHWA-D and 46 patients (15%) with sCAA died before 90 days. During a mean follow-up time of 5 ± 4 years (total 1,550 person-years), the incidence rate of recurrent ICH in patients with HCHWA-D was 20.9 vs 8.9 per 100 person-years in sCAA. Patients with HCHWA-D had a long-term mortality of 8.2 vs 8.4 per 100 person-years in patients with sCAA. After adjustments, patients with HCHWA-D had a higher risk of recurrent ICH (HR 2.8; 95% confidence interval 1.6–4.9; $p < 0.001$) and a higher long-term mortality (HR 2.8; 95% confidence interval 1.5–5.2; $p = 0.001$).

Conclusions: Patients with HCHWA-D have worse long-term prognosis after a first ICH than patients with sCAA. The absence of cardiovascular risk factors in most patients with HCHWA-D suggests that vascular amyloid is responsible for the recurrent hemorrhages. HCHWA-D is therefore a pure form of cerebral amyloid angiopathy with an accelerated clinical course and provides a good model to study the pathophysiology and future therapeutic interventions of amyloid-related hemorrhages. *Neurology*® 2016;87:1482–1487

GLOSSARY

APP = amyloid precursor protein; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **HCHWA-D** = hereditary cerebral hemorrhage with amyloidosis-Dutch type; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **sCAA** = sporadic cerebral amyloid angiopathy.

Spontaneous lobar intracerebral hemorrhage (ICH) involving the cortex or subcortical white matter accounts for $\approx 40\%$ of all spontaneous ICH.^{1,2} A common cause of lobar ICH, especially in the elderly, is cerebral amyloid angiopathy (CAA),^{3–5} which results from deposition of the β -amyloid protein in the media and adventitia of cortical and leptomeningeal arteries.⁴ In addition to being a common cause of ICH, CAA is an independent contributor to dementia.³ Neuropathologic studies have shown a prevalence of 55% to 59% of the sporadic form (sCAA) in patients with dementia and 28% to 38% in elderly patients without dementia.⁶ Currently, there is no specific therapy that can halt the progression of CAA or decrease the risk of ICH or dementia in affected individuals. Part of the problem in developing therapies stems from the fact

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that CAA-related clinical worsening occurs in older adults who often have interfering comorbidities that contribute to the outcome measures.

Hereditary cerebral hemorrhage with amyloidosis–Dutch type (HCHWA-D) is a genetic variant of CAA caused by a mutation at codon 693 of the amyloid precursor protein (APP) gene.^{7–10} This hereditary form of CAA occurs in several families originating from 2 coastal villages in the Netherlands.⁹ The mutation in HCHWA-D leads to extensive β -amyloid accumulation in the cortical and leptomeningeal arteries, resulting in amyloid deposits comparable to those in patients with sCAA.^{11,12} Like sCAA, HCHWA-D is characterized by recurrent ICHs and cognitive decline¹³; thus, it is considered a model for sCAA. Although previous studies shed light on the natural history of sCAA, the progression of HCHWA-D as it relates to mortality and ICH recurrence is not clear. Insight into the disease course of HCHWA-D not only will inform patients and clinicians about prognosis but also will give researchers insight into the usefulness of hereditary CAA as a model for the sporadic form.

We therefore aimed to compare the recurrent ICH rate and short- and long-term mortality rates after a first hemorrhagic event in patients with HCHWA-D and patients with sCAA.

METHODS Study design. We performed a multicenter cohort study by reviewing data from consecutive patients with HCHWA-D and sCAA presenting with a first spontaneous ICH.

Study population. We included patients with HCHWA-D presenting with a first spontaneous ICH to the Leiden University Medical Center between January 1992 and January 2015. Data on patients with HCHWA-D were retrieved from a prospective registry of all patients presenting with a spontaneous ICH to the Leiden University Medical Center. The HCHWA-D diagnosis was based on the presence of the APP mutation,¹⁰ pathologic examination confirming the diagnosis, or clinical symptoms suggestive of HCHWA-D (i.e., lobar ICH at a relatively young age) and a family history of HCHWA-D¹¹ if no genetic test or pathologic examination was performed.

We retrieved data on patients with sCAA from a prospective cohort of patients who presented with a first spontaneous ICH at the Massachusetts General Hospital in Boston between January 1993 and January 2012 and who were enrolled in a longitudinal cohort study of primary lobar hemorrhage.^{14,15} This group included consecutive patients ≥ 55 years of age with definite or probable sCAA diagnosed according to the previously validated Boston criteria.^{16,17} Probable CAA was diagnosed as multiple hemorrhagic lesions restricted to lobar, cortical, or cortico-subcortical

areas without another definite cause. We excluded patients with a diagnosis of inflammatory CAA.¹⁸

Standard protocol approvals, registrations, and patient consents. The study received approval from and was performed according to the guidelines of the institutional review boards of the Leiden University Medical Center and Massachusetts General Hospital.

Data collection. In the group with HCHWA-D, we obtained data on demographics and history of cerebrovascular risk factors, including hypertension, diabetes mellitus, and hypercholesterolemia, from medical records. The occurrence of hemorrhagic strokes (defined as the presence of clinical symptoms with acute hemorrhage documented by neuroimaging) also was obtained from the medical records. We interviewed patients who were alive at the time of the study and who had not visited the outpatient clinic in the past 12 months by telephone to verify baseline data and to answer questions about recurrence of lobar ICH. If they reported a recurrent ICH, we reviewed clinical charts and CT reports to confirm the new event. We obtained date and cause of death by reviewing the clinical chart or consulting the general practitioner if necessary.

In the sCAA group, collection of baseline data was performed as previously described.¹⁹ At hospital admission, we obtained a full medical history (including history of hypertension, diabetes mellitus, and hypercholesterolemia) and performed a neurologic examination. Through periodic follow-up phone interviews, we acquired information on recurrence of lobar ICH and death.²⁰ If patients reported a new ICH, the clinical charts were reviewed to confirm the new event. We acquired the date of death by checking the Social Security Death Index.²¹ Some of the baseline and follow-up data of this well-characterized sCAA cohort were previously published.¹⁴

Radiologic data. In patients with HCHWA-D and sCAA, we assessed the location and the number of hemorrhages on baseline CT scan images. All (recurrent) hemorrhages were confirmed by CT images or CT reports. If the source images of the CT scan were not available, we obtained the location and number of hemorrhages from the radiology report. MRI acquisition and analyses used in the sCAA cohort have been described previously.¹⁴

Statistical analysis. Patients with HCHWA-D and sCAA were followed up from their first ICH until the occurrence of recurrent ICH, death, or the end of follow-up, and the mean follow-up time was calculated. Short-term mortality was defined as death ≤ 90 days after the first ICH. Follow-up time for recurrent ICH started directly after the patient presented with ICH. Follow-up data of patients who survived the first 90 days after the first ICH were used to determine long-term mortality (follow-up time for long-term mortality started at 90 days after presentation with ICH). We calculated the incidence rates of recurrent ICH and death using the occurrence of an event per 100 person-years of follow-up. To study the differences in recurrent ICH and long-term mortality between patients with HCHWA-D and sCAA, we performed univariable and multivariable Cox regression analyses, calculating hazard ratios (HRs) with 95% confidence intervals (CIs). In the multivariable analyses, we adjusted for age and sex. We used Kaplan-Meier curves for visualization of the follow-up data. We performed separate analyses excluding patients with HCHWA-D without confirmed APP mutation. Time intervals between consecutive hemorrhages in the patients with HCHWA-D were analyzed for a correlation with a generalized estimating equation model. This manuscript was prepared in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.²²

RESULTS First ICH. We included 58 patients with HCHWA-D and 316 patients with sCAA who presented with a first ICH. In the group with HCHWA-D, 32 patients had a confirmed APP mutation, 5 had a diagnosis by analysis of pathology specimens, and 21 had symptoms and a family history of HCHWA-D. Of these 58 patients, 8 patients (14%) did not survive the first 90 days after presenting with ICH. In the sCAA group, 46 patients (15%) did not survive the first 90 days after their index ICH, and 30 patients did not consent for the longitudinal follow-up cohort study. These patients did not differ in baseline characteristics from the other patients with sCAA, as previously described.¹⁴ Patients with HCHWA-D and sCAA had a mean follow-up time of 5 ± 4 years and a total follow-up time of 1,550 person-years.

Table 1 shows the baseline demographics, vascular risk factors, and radiologic characteristics of both groups. Patients with HCHWA-D were younger at presentation (54 ± 8 vs 72 ± 9 years) and less often had a history of hypertension, diabetes mellitus, or hypercholesterolemia. In the patients with HCHWA-D, the majority of hemorrhages were located in the occipital lobe (35%). Four patients (6%) with HCHWA-D

presented with multiple, simultaneous hemorrhages. In the sCAA group, the majority of hemorrhages were located in the frontal lobe (33%), and 19 patients (8%) had multiple hemorrhages on presentation.

Recurrent ICH. During follow-up, 38 patients with HCHWA-D (76%) and 86 patients with sCAA (36%) developed a recurrent ICH (20.9 vs 8.9 per 100 person-years, figure 1A). Table 2 shows the details of the incident rates and HRs of the events. After adjustment for age and sex, the risk of recurrent ICH in patients with HCHWA-D remained higher than in patients with sCAA (HR 2.8, 95% CI 1.6–4.9, $p < 0.001$). In separate analyses including only patients with HCHWA-D with a confirmed APP mutation, the HR remained essentially the same (adjusted HR 2.4, 95% CI 1.3–4.7, $p = 0.008$).

In total, 24 patients with HCHWA-D (48%) had >1 recurrent hemorrhage during follow-up, whereas none of the 86 patients with sCAA developed >1 recurrent hemorrhage. The number of recurrent hemorrhages in the patients with HCHWA-D was highly variable. In the 50 survivors, the number of recurrences varied as follows: 0 in 12 patients, 1 in 13 patients, 2 in 11 patients, 3 in 8 patients, 4 in 2 patients, 5 in 1 patient, 6 in 1 patient, and 7 in 2 patients. Sample CT scans of a patient with HCHWA-D with multiple recurrent hemorrhages are shown in figure 2. Two patients with HCHWA-D and 1 patient with sCAA had a recurrent hemorrhage only 2 months after the presenting ICH. The mean time between the index hemorrhage and the first recurrence was 3.1 years in patients with HCHWA-D and 4 years in patients with sCAA. The time intervals between ICH recurrences in the patients with HCHWA-D with multiple recurrent hemorrhages seemed to decrease after every new bleed in the first couple of recurrences ($p = 0.076$, figure 3). Six of the first recurrent hemorrhages in HCHWA-D (16%) were in the same location as the first ICH. Five of the second recurrent hemorrhages (21%) were in the same location as the first or second ICH. Three of the third recurrent hemorrhages (23%) were in the same location as the previous hemorrhages.

Mortality. Of the 50 patients with HCHWA-D and 240 patients with sCAA who survived the first 3 months, 24 patients with HCHWA-D (48%) died during the long-term follow-up compared with 105 patients with sCAA (44%; 8.2 vs 8.4 per 100 person-years, figure 1B). Univariable Cox regression analysis showed no significant difference in mortality. However, after adjustment for age and sex, patients with HCHWA-D had a significantly higher case-fatality rate (HR 2.8, 95% CI 1.5–5.2, $p = 0.001$). There were no differences in case-fatality rates between

Table 1 Clinical and radiological characteristics

	Patients presenting with HCHWA-D (n = 58), n (%)	Patients presenting with sCAA (n = 316), n (%)
Men	28 (48)	162 (51)
Age at first ICH, y	54 ± 8	72 ± 9
Hypertension	10 (17)	194 (61)
Hypercholesterolemia	3 (5)	136 (43)
Diabetes mellitus	3 (5)	55 (17)
Radiologic markers		
Affected hemisphere		
Right	28 (48)	114 (48)
Left	28 (48)	105 (44)
Both	2 (4)	19 (8)
First ICH location		
Frontal	11 (19)	78 (33)
Parietal	12 (21)	44 (18)
Temporal	11 (19)	56 (23)
Occipital	20 (35)	39 (16)
Cerebellar	0 (0)	3 (1)
Other	0 (0)	1 (0)
Multiple hemorrhages	4 (6)	19 (8)

Abbreviations: HCHWA-D = hereditary cerebral hemorrhage with amyloidosis-Dutch type; ICH = intracerebral hemorrhage; sCAA = sporadic cerebral amyloid angiopathy. Age is given as mean $\pm$ SD. In the group with HCHWA-D, 2 patients had missing data on cardiovascular risk factors. In the sCAA group, only the ICH location of the 240 ICH survivors was available.

Table 2 Incidence rates and hazard ratios (HRs) for recurrent intracerebral hemorrhage (ICH) and mortality during follow-up

	Patients with HCHWA-D (n = 50)	Patients with sCAA (n = 240)	p Value
Event: occurrence of recurrent lobar ICH			
Total observed person-years	182	968	...
Occurrences, n (%)	38 (76)	86 (36)	...
Incidence ICH per 100 person-y (95% CI)	20.9 (14.2–27.5)	8.9 (7.1–11)	...
Crude hazard ratio (95% CI)	2.4 (1.6–3.6)	Referent	<0.001
Adjusted hazard ratio ^a (95% CI)	2.8 (1.6–4.9)	Referent	<0.001
Event: occurrence of death ≥90 d			
Total observed person-years	293	1,257	...
Occurrences, n (%)	24 (48)	105 (44)	...
Incidence death per 100 person-y (95% CI)	8.2 (4.9–11.5)	8.4 (6.9–10.1)	...
Crude HR (95% CI)	1.0 (0.6–1.5)	Referent	0.873
Adjusted HR ^a (95% CI)	2.8 (1.5–5.2)	Referent	0.001

Abbreviations: CI = confidence interval; HCHWA-D = hereditary cerebral hemorrhage with amyloidosis-Dutch type; HR = hazard ratio; ICH = intracerebral hemorrhage; sCAA = sporadic cerebral amyloid angiopathy.

^aAdjusted for age and sex.

men and women in both patients with HCHWA-D (HR 1.19, 95% CI 0.53–2.66, $p = 0.68$ for women vs men) and patients with sCAA (HR 0.90, 95% CI

0.61–1.32, $p = 0.59$ for women vs men). A separate comparison of confirmed mutation carriers to patients with sCAA showed essentially the same results (adjusted HR 2.2, 95% CI 1.1–4.6, $p = 0.03$). Causes of death in patients with HCHWA-D included a recurrent ICH in 19 patients (82%) and sepsis (4%) in 1 patient. In 3 patients with HCHWA-D, the cause of death was unknown.

DISCUSSION Our results show that patients with HCHWA-D have an accelerated clinical course after a first symptomatic hemorrhage compared with patients with sCAA. Despite the fact that patients with sCAA have a considerable risk of recurrent ICH, patients with HCHWA-D have an almost 3 times higher risk of developing a recurrent hemorrhage after adjustment for age and sex. During a relatively short follow-up time of 5 years, 3 of 4 patients with HCHWA-D and 1 of 3 patients with sCAA developed a recurrent ICH. Additionally, patients with HCHWA-D who presented with an ICH have a nearly 3 times higher long-term case-fatality rate compared with patients with sCAA when adjusted for age and sex. Only a minority of patients with HCHWA-D had a history of cardiovascular risk factors, whereas patients with sCAA often had hypertension, diabetes mellitus, or hypercholesterolemia. Although this may

Figure 1 Cumulative percentage of recurrent intracerebral hemorrhage (ICH; A) and death ≥90 days (B)

HCHWA-D, hereditary cerebral hemorrhage with amyloidosis-Dutch type; sCAA, sporadic cerebral amyloid angiopathy.

Figure 2 CT scans of a patient with hereditary cerebral hemorrhage with amyloidosis–Dutch type with recurrent hemorrhages

be due in part to the lower age in patients with HCHWA-D, the absence of cardiovascular risk factors in most patients with HCHWA-D suggests that the vascular amyloid accumulation is the major contributor to adverse outcomes.

Our results are in line with previous studies that found that patients with HCHWA-D who survive after ICH have a high risk of recurrent ICH with

Figure 3 Time interval between consecutive hemorrhages in patients with hereditary cerebral hemorrhage with amyloidosis–Dutch type

Two outliers (interval of 17 years in the first category and 12 years in the third category) are not depicted in this figure (1st-2nd means time interval between the first and second hemorrhage, 2nd-3rd means time interval between the second and the third hemorrhage, etc).

a great variation in the number of recurrences.⁸ The exact mechanisms of this worse disease course in HCHWA-D are unclear. Patients with HCHWA-D may have a higher burden of small-vessel disease at the moment of their first ICH compared with patients with sCAA. Unfortunately, we did not systematically obtain MRIs in the HCHWA-D cohort to make this comparison with patients with sCAA. Another possibility might be that amyloid depositions in patients with HCHWA-D accumulate not only at an earlier age but also more rapidly than in patients with sCAA, causing a higher burden of amyloid angiopathy in the vessels. This might be reflected by the finding that the intervals between recurrent hemorrhages seem to become smaller over time, although this trend was not statistically significant. This hypothesis could eventually be tested with Pittsburgh compound B PET studies or by monitoring CSF β -amyloid levels.

The variation in phenotype in patients with HCHWA-D all carrying the same mutation suggests that additional environmental or genetic factors or a combination of both influences vascular risk and plays a role in ICH development in hereditary amyloid angiopathy. In a previous study in 187 members of 4 large families with HCHWA-D, female sex was identified as a possible risk factor (relative risk 1.7, 95% CI 1.2–2.5 in women vs men) for mortality in HCHWA-D.²³ In the present study, which included a smaller cohort, however, we could not confirm this association.

Our study has several limitations. First, our sample size is small, which limited our ability to look in detail at factors that influence ICH recurrence such as cardiovascular risk factors. Our study nevertheless has follow-up data of the largest cohorts of patients with sCAA and HCHWA-D to date. Second, we could not confirm the presence of the APP mutation in all patients with HCHWA-D. Oftentimes, individuals from families with HCHWA-D choose to remain unaware of their mutation status.¹¹ However, in additional analyses including only patients with HCHWA-D with a confirmed mutation, our results remained the same. Third, the data of the HCHWA-D cohort were collected in part from medical records, which might have led to underestimation of the number of ICH recurrences. We know that patients with HCHWA-D do not necessarily go to the hospital when they suspect they have had a new ICH if the symptoms are mild. The difference between sCAA and HCHWA-D recurrences might therefore be even more pronounced than our results suggest. Furthermore, patients with HCHWA-D might have visited other regional hospitals without our knowledge. We expect, however, that this number is small because we interviewed all living patients by telephone and because

the Leiden University Medical Center is the regional referral center for HCHWA-D and the majority of patients live in the area. In any case, underestimation of ICH recurrence in HCHWA-D would only make our findings stronger. Finally, we did not have uniform data on smoking for both cohorts. Future studies should prospectively record vascular risk factors, including smoking, because they might contribute to the progression of the disease.

HCHWA-D can be considered a pure form of CAA with an accelerated clinical course. Because of its progressive course with a high number of recurrent ICH and its variation in phenotypic expression, it may serve as a good model to investigate additional disease-modifying factors and therapeutic strategies for CAA.

AUTHOR CONTRIBUTIONS

Design and conceptualization of the study: E.S.v.E., M.E.G., J.v.d.G., M.A.v.B., G.M.T., S.M.G., M.J.H.W. Acquisition, analysis, or interpretation of the data: E.S.v.E., K.M.S., A.M.A., J.R., M.E.G. Data management: E.S.v.E., A.A., K.M.S. Drafting or revising the manuscript: E.S.v.E., M.E.G., J.H., A.V., A.A., G.M.T., M.J.H.W.

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DISCLOSURE

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