Staging cerebral amyloid angiopathy: from marker to model

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PART I

Clinical signs and symptoms of cerebral amyloid angiopathy

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MIGRAINE WITH AURA AS EARLY DISEASE MARKER IN HEREDITARY DUTCH-TYPE CEREBRAL AMYLOID ANGIOPATHY

Chapter 2 | Migraine with aura as early disease marker in Hereditary Dutch-type Cerebral Amyloid Angiopathy

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Abstract

Background and purpose: To determine whether migraine, which has often been described as an inaugural manifestation in monogenic cerebrovascular syndromes, is associated with cerebral amyloid pathology we assessed migraine and its correlation with MRI markers in Hereditary Dutch-type Cerebral Amyloid Angiopathy (D-CAA or HCHWA-D).

Methods: All D-CAA mutation carriers who visited our clinic between 2012-2018 were included. Migraine was diagnosed by an interview and classified according to the International Classification of Headache Disorders. MRIs were scored for intracerebral hemorrhage (ICH) location(s) and presence of cortical superficial siderosis (cSS). Kaplan Meier survival analysis was used for age of ICH onset in carriers with and without migraine. Correlation with ICH location(s) and cSS were calculated with Poisson regression analysis adjusted for confounders.

Results: We included 86 D-CAA mutation carriers (57% women, mean age 57 years), 48 (56%) suffered from migraine, all with aura. Prevalence was higher than expected compared with the general population (women $p<0.05$; men $p<0.001$). Migraine was the inaugural symptom in 77% and an isolated symptom in 35% of the carriers. Carriers with and without migraine did not differ for age of first ICH, cSS prevalence or occipital ICH. Time between migraine onset and first ICH was 8.5 years. Aura attacks lasting ≥60 minutes signaled acute ICH in 55%.

Conclusions: Migraine with aura is an important, often inaugural symptom in D-CAA. Aura attacks lasting ≥60 minutes may signal acute ICH in D-CAA. Migraine with aura may be regarded as an early marker of disease in hereditary CAA preceding the occurrence of symptomatic ICH by several years.

Introduction

Cerebral amyloid angiopathy (CAA) is an important cause of intracerebral hemorrhage (ICH) in elderly.[1] CAA patients often report Transient Focal Neurological Episodes (TFNE), which are typically recurrent stereotyped attacks that are strongly related with cortical superficial siderosis (cSS).[2] The definitions of TFNE and migraine aura, described as 'positive, reversible neurological symptoms in a sequential pattern' according to the International Classification of Headache Disorders 3rd edition, overlap.[3]

The relationship between migraine and cerebrovascular disease has long been recognized, but the underlying pathophysiological basis is still not understood.[4, 5] Migraine has been described in rare monogenic cerebrovascular syndromes as an early hallmark or even isolated symptom, for instance in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and Retinal Vasculopathy with Cerebral leukoencephalopathy and Systemic manifestations (RVCL-S), suggesting a link between migraine and microvascular changes in early stages of angiopathies.[6-8]

Migraine has been reported in CAA, however not much is known about the prevalence and characteristics.[9] Hereditary Dutch-type Cerebral Amyloid Angiopathy (D-CAA, also called Hereditary Cerebral Hemorrhage with Amyloidosis-Dutch type, HCHWA-D) is an hereditary variant of CAA, caused by a mutation in the Aβ region of the amyloid precursor protein (APP) gene. D-CAA patients suffer from recurrent ICH from the age of 50. The pathophysiology of D-CAA and sporadic CAA are similar, allowing D-CAA to function as a model of CAA, enabling investigation of early disease stages.[10-13]

This study investigates migraine prevalence and symptomatology in D-CAA, relating migraine history to ICH onset, ICH location and presence of cSS on MRI.

Methods

For this retrospective study we retrieved patient files of all D-CAA mutation carriers who visited the Cerebral Hereditary Angiopathy outpatient clinic or the inpatient clinic of our neurology department at the Leiden University Medical Center (LUMC), the Dutch national referral center for D-CAA, between January 2012 and January 2018. Files were collected in August 2018. All available information up to this date was used for the analysis. The diagnosis D-CAA carrier was made based on DNA analysis of the Glu693Gln mutation in the APP gene, or if no DNA analysis was performed, a medical history with one or more ICHs with CAA characteristics

according to the Boston criteria on MRI and a positive family history for D-CAA.[14] In this study, the participants are called ICH carriers if they had at least one symptomatic ICH, and non-ICH carriers if they did not have a symptomatic ICH. All patients underwent a semi-structured headache questionnaire. Patients who had visited our hospital and of whom no information on migraine and headache was available were asked to take this structured headache questionnaire via a telephone interview if they had consented to be contacted for participation in scientific research before. The questionnaire contained questions on migraine and headache characteristics, attack frequency and duration, aura characteristics, and age of onset. Furthermore, it contained questions about Transient Focal Neurological Episodes (TNFE) and epilepsy. The presence, time course and clinical characteristics of migraine were assessed by a neurologist or resident in neurology and a final diagnosis was made by a neurologist specialized in migraine (G.M.T). Migraine was defined according to the ICHD-3 criteria and classified as definite or probable migraine, and the subtypes migraine with aura or migraine without aura. Aura without (migraine) headache was also defined according to the ICHD-3 edition as migraine with aura.[3] In addition to migraine history, information on other headache subtypes was captured.

The dataset analyzed in this study is not publicly available because of restricted access and privacy legislation but further information about the dataset is available from the corresponding author on reasonable request. Approval for this study has been granted by the local ethics review board of the Leiden University Medical Center, who waived the need for written informed consent from individual participants for the study. The telephone interviews were only conducted in participants who had given previous written informed consent to be contacted for participation in scientific research.

MRI analysis

All latest available 3 and 1.5 Tesla MRI scans of the brain were retrieved and presence of cSS and ICH was scored by two independent observers (E.K. and S.V.). ICH was defined as large, irregular areas of signal void which are visible on T1-weighted and T2-weighted sequences, according to the STRIVE criteria.[15] Location of ICH was classified as occipital or non-occipital (frontal, parietal, temporal, infratentorial). We looked at occipital ICH specifically since it is known that this lobe is most severely affected with amyloidosis in CAA and HCHWA-D.[16] cSS was defined as linear hemosiderin deposits within the subarachnoid space, leptomeninges and the superficial layers of the cerebral or cerebellar

cortex.[17] One important criterion for the identification of cSS in sporadic CAA is that it should be separated from any lobar ICH by at least 3 unaffected sulci.[18] However, in D-CAA, due to the large number of ICHs in each individual, this makes the identification of cSS almost impossible. Therefore, in this study we scored cSS as either ≤3 sulci from an ICH or >3 sulci from an ICH, to prevent under recognition of cSS in D-CAA. cSS was scored on susceptibility weighted imaging sequences (SWI) or T2*-weighted imaging sequences. In case of non-concordance, findings were discussed with a third observer with >15 years of experience in the field (M.v.W) in order to achieve consensus.

Statistics

Descriptive statistics were performed. Between carriers with and without migraine, difference in proportion of non-ICH mutation carriers and ICH mutation carriers, occipital ICH and cSS on MRI was assessed by Poisson regression analysis corrected for age and sex. Interobserver variability (kappa value) was calculated for the MRI markers occipital ICH and cSS, the grading of interobserver agreement was performed according to the recommendations of Landis and Koch.[19] Relative risks (RR) with 95% confidence intervals were calculated. The difference in age at which the first ICH occurred in mutation carriers with and without migraine, as well as in mutation carriers with early and late onset migraine, was assessed with a Kaplan Meier survival analysis. Late onset migraine was defined as occurring after the third decade, based on earlier studies.[20] In order to compare the prevalence of migraine in D-CAA to the prevalence in the Dutch population we used data from a large population-based cohort study: the Genetic Epidemiology of Migraine (GEM) study.[21] Life-time prevalence of migraine in D-CAA was calculated separately for men and women. Prevalence of migraine in the general Dutch population was calculated by using the age specific life-time prevalence tables of the GEM study for men and women separately. We fitted a logistic regression model to the combined data with main effects for cohort (D-CAA/general Dutch population) and age, and their interaction. We did this for men and women separately. In both models we tested for any difference between the cohorts by means of a Chi-square test.

Results

Between January 2012 and January 2018, 95 D-CAA mutation carriers visited the LUMC, all of whom were included in this study. Of 19 patients no information on migraine was available, ten of these 19 patients had given permission to be

contacted for participation in scientific research and were contacted and participated in a telephone interview. Of the nine remaining patients five were deceased and four patients had not given permission to be contacted for participation in research. Of the 86 carriers with a known migraine status the mean age was 57 years, 57 (66%) suffered at least one symptomatic ICH, and 49 (57%) were women (Table 1). Eight patients were deceased at the time of analysis, for these patients age at time of death was used for the age calculation. In 71 carriers the diagnosis D-CAA was confirmed by DNA analysis. The remaining 15 carriers had at least one ICH with CAA characteristics on MRI in combination with a positive family history of D-CAA.

Migraine symptoms

Among the 86 carriers with D-CAA and a known migraine status, 48/86 (56%) had a positive history of migraine, the majority of whom were women (29/48, 60%). According to the ICHD-3 criteria, 39/86 (45%) had definite migraine and 9/86 (10%)

Table 1: Demographics and characteristics.

		D-CAA patients* (n=86)
Mean age in years† (range)		57 (31-84)
Women (%)		49 (57)
DNA proven (%)		71 (83)
Symptomatic ICH (%)		57 (66)
Mean age at first ICH in years (n=57) (range)		55 (35-78)
Epilepsy (%)		23 (27)
	Generalized	10 (12)
	Focal without loss of consciousness	2 (2)
	Focal with loss of consciousness	5 (6)
	Mixed focal and generalized attacks	5 (6)
	Unknown type	1 (1)
Previous or persisting psychiatric or mood disturbances‡ (%)		35 (41)
Transient Focal Neurological Episodes (TFNE) (%)		6 (7)

**D-CAA patients are defined as: 1) DNA proven (positive DNA analysis for codon 693 mutation in the amyloid-β precursor protein (AβPP) gene) or 2) symptomatic lobar ICH with characteristics of CAA on MRI and positive family history, or 3) both.*

†For patients that were deceased at the moment of analysis (n=8) age at time of death was used for the calculation.

‡Including symptoms of depression and anxiety, ADHD, psychosis, PTSS and burn-out.

probable migraine (Table 2). All carriers with migraine suffered from the subtype migraine with aura, all reported visual aura symptoms, 36/86 (42%) patients had visual auras only, 10/86 (12%) additional sensory aura symptoms, and 4/86 (5%) additional aphasia (Table 2). Typical aura without headache occurred in 21/86 (24%) of patients, in 12/86 (14%) of patients this was the only type of migraine attacks they experienced. Of the carriers, 11/86 (13%) reported both attacks with and without aura.

Table 2: Migraine and headache characteristics.

		D-CAA patients (n=86)
Lifetime prevalence of Migraine (%)*	Probable	9 (10)
	Definite	39 (45)
	In men (n=37)	19 (51)
	In women (n=49)	29 (59)
Mean onset age of migraine in years (range)†		37 (9-69)
Migraine subtypes (%)	Migraine with aura attacks total	48 (56)
	Migraine with aura only	37 (43)
	Migraine with and without aura‡	11 (13)
	Migraine without aura attacks only	0 (0)
	Migraine without headache only	12 (14)
Migraine characteristics (%)	Headache	36 (42)
	Hemicranial	12 (14)
	Pulsatile	10 (12)
	Photophobia	23 (27)
	Phonophobia	19 (22)
	Nausea	23 (27)
	Vomiting	12 (14)
Migraine attack frequency (%)	<1 attack/year	9 (10)
	1-4 attacks/year	7 (8)
	5-7 attacks/year	3 (3)
	8-12 attacks/year	9 (10)
	>12 attacks/year	15 (17)
	Unknown	5 (6)

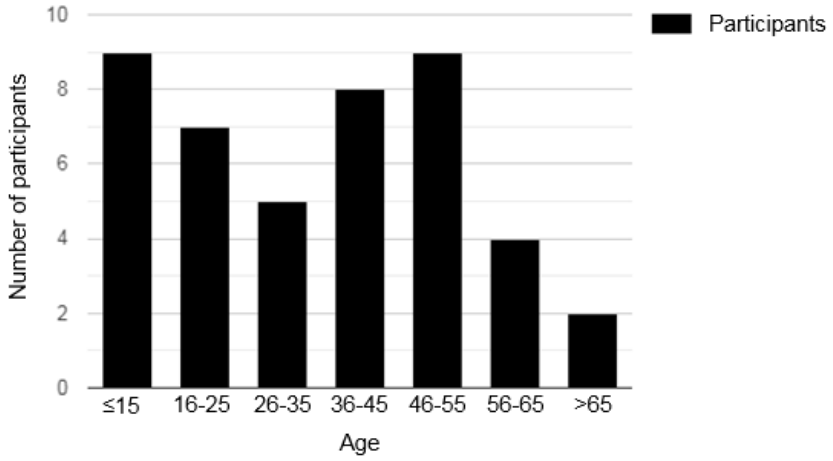
Migraine attack duration (%)	<1 day	26 (30)
	1-2 days	4 (5)
	3-5 days	6 (7)
	Unknown	12 (14)
Aura subtypes (%)	Visual only	36 (42)
	Visual and sensory only	8 (9)
	Visual and aphasia only	2 (2)
	Visual, sensory and aphasia	2 (2)
Long lasting aura‡ (%)		11 (13)
Other headache types (%)	Tension-type headache (TTH)	24 (28)
	Migraine and TTH	11 (13)
	Medication-overuse headache (MOH)	1 (1)
	Migraine and MOH	1 (1)
	MOH and TTH	6 (7)
	Migraine, MOH and TTH	4 (5)
	Unclassifiable	2 (2)

**Defined according to The International Classification of Headache Disorders, 3rd edition.*
†N=42. Two patients described the onset as 'during childhood', these were excluded from the calculation.
‡Defined according to ICHD-3 one single aura symptom lasting >60 minutes.

The age at onset of migraine with aura showed two peaks; one before the third decade and one after the fourth decade (Figure 1). Prevalence of migraine in D-CAA was higher for men ($p<0.001$) and women ($p=0.038$) compared with the prevalence in the general Dutch population (also own data from the GEM study, which found a lifetime prevalence of migraine of 13% in men and 33% in women).[21]

Carriers with migraine were not older than those without migraine, nor was there a difference in medical history between the groups (Table 3). The majority of carriers with migraine had their first attack before they had the first symptomatic ICH, 37/48 (77%), and for 17/48 (35%) it was an isolated symptom. The median time between migraine onset and first ICH was 8.5 years (range: 3-46).

Figure 1: Age at onset of migraine with aura.



N=44, 26 women, 18 men (all with known migraine). Four participants were excluded due to unknown age of onset of migraine. Two patients described migraine with aura onset as 'during childhood', these patients were placed in the ≤15 category.

Table 3: Characteristics of D-CAA mutation carriers with migraine compared with D-CAA mutation carriers without migraine.

	Migraine* (n=48)	No migraine (n=38)	RR (95% CI)
Mean age in years† (range)	58 (31-84)	57 (35-75)	
Women (%)	29 (60)	20 (53)	
Symptomatic ICH (%)	31 (65)	26 (68)	1.00 (0.59-1.7)
T1/T2 weighted MRI	(n=40)	(n=30)	
ICH on MRI (%)	32 (80)	22 (73)	1.12 (0.64-1.95)
Occipital ICH (%)	25 (63)	17 (57)	1.23 (0.65-2.31)
SWI/T2*-weighted MRI	(n= 38)	(n=24)	
cSS on MRI (%)	17 (45)	10 (42)	1.17 (0.52-2.64)‡
cSS >3 gyri separated from ICH (%)	5 (13)	6 (25)	0.57 (0.17-1.92)

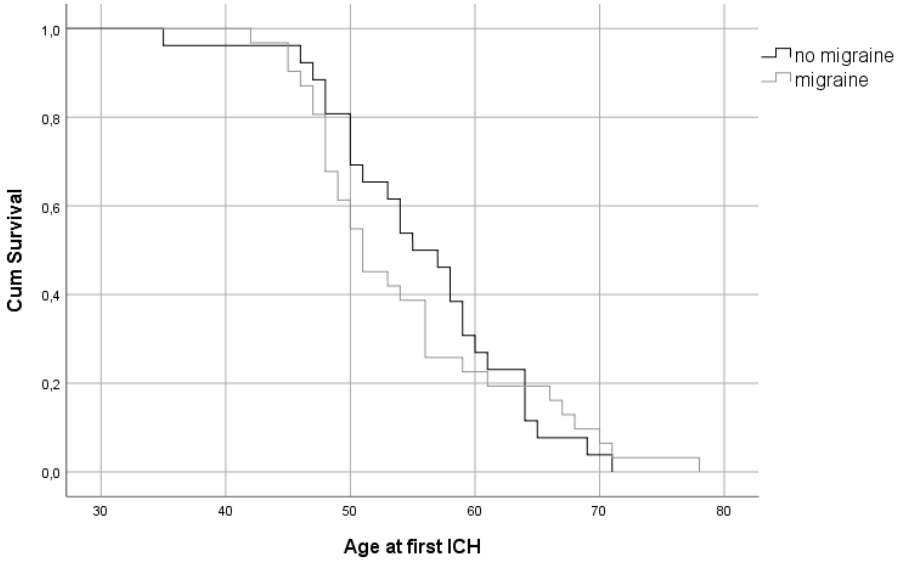
Total number of mutation carriers n=86, for n=16 no T1/T2 weighted MRI data were available, for n=24 no SWI/T2 weighted MRI data were available.*

**Certain + probable migraine.*

†For patients that were deceased at the moment of analysis (n=8) age at time of death was used for the calculation.

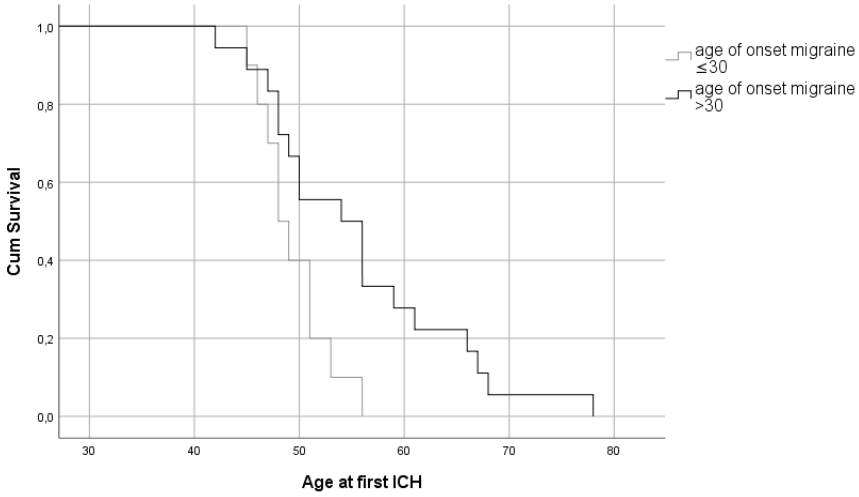
‡If we compared patients with MA without headache only (n=12): RR 0.95 (0.33-2.78).

Figure 2: *Age at first ICH for patients with and without migraine.*



Migraine n=31, 31 events, no migraine n=26, 26 events. Mean age at first ICH for patients with migraine 54 years (95% CI 51-58), for patients without migraine 56 years (95% CI 53-59), P=0.749 (Log Rank test).

Figure 3: Age at first ICH for patients with early and late onset migraine.



Early onset migraine n=10, 10 events, late onset migraine (onset after the age of 30) n=18, 18 events. Mean age at first ICH for patients with early onset migraine 49 years (95% CI 47-51), for patients with late onset migraine 56 years (95% CI 51-60), P=0.024 (Log Rank test).

The mean age at which ICH carriers with migraine experienced their first ICH did not differ from those without migraine (Figure 2). Mutation carriers with an onset of migraine on or before the third decade experienced their first ICH at a significantly earlier age compared with mutation carriers with migraine onset after the third decade (Figure 3).

Out of all patients with migraine, 11/48 (23%) had experienced migraine attacks with visual, single aura symptomatology lasting over 60 minutes. For 6/11 (55%) of the cases this was directly prior to a symptomatic ICH confirmed on the CT scan. For one mutation carrier of the six this was the first experienced migraine attack, for five of the carriers this was the first time they experienced an ICH. In four of the six carriers the hemorrhage was located in the occipital lobe.

Hemorrhage location and cortical superficial siderosis on MRI

Among the 86 carriers with D-CAA and a known migraine status, for 62 the presence of cSS could be scored on 1.5 or 3 Tesla MRI with SWI or T2*-weighted images. cSS was found in 27/62 (44%) of the carriers, 16/62 (26%) had cSS only ≤3 gyri of ICH, 2/62 (3%) had cSS only >3 gyri of ICH, and 9/62 (15%) carriers had cSS both ≤3 gyri and >3 gyri of ICH (Table 3). The interobserver agreement for cSS was very high (β =0.91). There was no difference in the presence of cSS on MRI for patients with migraine compared to those without migraine (p=0.702, RR 1.17 (95% CI 0.52-2.64)), nor was there a difference if cSS was scored only if it was separated from ICH by at least 3 gyri (p=0.361, RR 0.57 (95% CI 0.17-1.92)). As the definition of typical aura without headache comes closest to the definition of TFNE, we compared cSS occurrence on MRI in patients with typical aura without headache only, to patients with migraine headache and patients without migraine and did not find a difference (p=0.931, RR 0.95 (95% CI 0.33-2.78)). In 70 patients T2 or T1 weighted images were available for analysis of presence and location of ICH. Occipital ICH was found in 42/70 (60%) of the patients. The interobserver agreement for occipital ICH was substantial (β =0.83). There was no significant difference in the presence of occipital ICH in patients with or without migraine (p=0.531, RR 1.23 (95% CI 0.65-2.31)).

Discussion

In this study we found that more than half of D-CAA patients had migraine, 51% of men and 59% of women, all of them with visual aura. This prevalence is much higher than expected in the general population.[21-23] Migraine attacks preceded the

first symptomatic hemorrhage in the majority of carriers but did not seem to be a predictor for an earlier onset of first hemorrhage. However, migraine onset on or before the third decade was associated with an earlier onset of the first hemorrhage in D-CAA. Single aura symptomatology lasting more than 60 minutes occurred in 23% of the patients with migraine, similar to a recent study that showed prolonged aura to be quite common in the general population.[24] Nevertheless, it was an alarming symptom as it was a sign of acute ICH in 55% of our D-CAA carriers with long lasting aura. Age of onset of migraine aura in D-CAA occurred in two peaks, with more than half of the patients experiencing their first migraine attack after the third decade and a mean age of onset which is higher than expected in the general population.[25] Migraine with aura was not related to occipital ICH or cSS on MRI. We have not found any proof that migraine without aura is related to HCHWA-D.

Beside hemorrhagic events and cognitive decline, TFNEs are a common symptom of CAA. TFNEs are defined as 'recurrent, stereotyped, spreading paraesthesiae or other transient focal neurological symptoms (such as weakness, dysphasia) which last several minutes'.[26, 27] TFNEs with visual disturbances are also described in literature, occurring in 14-16% of TFNEs.[28, 29] The definition of aura in migraine overlaps with that of TFNE, which might raise the question whether what is termed as typical migraine aura in D-CAA may also be labelled as TFNE. It is, however, not possible to differentiate between the two phenomena based on the symptomatology. TFNE is strongly associated with cSS on MRI, whereas in our study migraine there was no clear association between the presence of cSS. Although criteria for identifying cSS on MRI in sporadic CAA are well known and have been tested multiple times, these criteria are not usable for D-CAA, as due to the large number of ICH in D-CAA, cSS is almost always within 3 gyri of an ICH.[17, 18] We considered it, therefore, necessary to use also an additional scoring system for cSS in D-CAA, in order to avoid under-diagnosis of cSS in patients with D-CAA.

Migraine aura attacks are thought to be a result of cortical spreading depression.[30] Interestingly, migraine with aura is one of the early characteristics of other small vessel diseases such as CADASIL and RVCL. In these monogenic angiopathies the migraine prevalence is higher than in the general population and an early hallmark of the disease, occurring before the first cerebrovascular event.[6, 8] Our study in D-CAA shows two peaks in age of onset: a first one before the third decade which is comparable to onset of migraine with aura in the general population, and a second peak occurring after the fourth decade.[31] Late-life migraine with aura is also found in CADASIL and has been described in sCAA, and might be a sign of increasing disease pathology.[9, 20] The high prevalence of migraine with aura in D-CAA might partially be explained by

a familial clustering of migraine apart from D-CAA. However, the occurrence of visual aura attacks as a symptom of a new intracranial hemorrhage and the association of early onset migraine to earlier occurrence of first ICH does suggest a link to CAA pathology. The presence of migraine in angiopathies such as CADASIL, RVCL and D-CAA suggests that it may be caused by vascular changes associated with damage to the intracerebral small vessels leading to impaired vasoreactivity and increased susceptibility for cortical spreading depression, which has been shown in earlier studies in mouse-models.[32] Further studies on migraine in hereditary cerebral angiopathies might increase the understanding of migraine pathophysiology in general.

Our study has some limitations. Our study population was relatively small due to the rarity of the genetic disease D-CAA. Nevertheless, as D-CAA forms a unique possibility to study the early phases of CAA, research in this relatively small population may provide important insights in the pathophysiology of CAA. Another limitation of this study is that some data were missing as carriers had passed away. Furthermore, as the data were retrieved retrospectively, our data are subjected to recall bias, especially in the D-CAA patients with cognitive symptoms. Therefore, we could not reliably investigate migraine trigger factors in this population. Lastly, the timing of the MRI images did often not correspond to the onset of migraine attacks nor did all carriers get an MRI at the same field strength and around the same time, as scans that were made over the years for clinical reasons. Therefore, our results concerning the relationship between cSS and ICH should be considered with caution. Furthermore, we only investigated the location of ICH and the presence of cSS and did not investigate the association between migraine and other CAA markers in detail.

Our study shows that migraine with aura may be regarded as an early marker of disease in hereditary CAA. Further prospective studies are needed to confirm our findings, to determine whether migraine with aura is also a frequent symptom in sporadic CAA and to unravel its underlying pathophysiology in relation to small vessel damage.

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