Clinical-radiological presentation and natural history of iatrogenic cerebral amyloid angiopathy

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Abstract

Background: We aimed to describe neuroimaging features, clinical profiles and long-term outcomes in patients with iatrogenic cerebral amyloid angiopathy (iCAA).

Methods: We performed a systematic literature search for case series of iCAA and included individual patients and their longitudinal clinical and neuroimaging data in this pooled cohort study. Patients meeting a modified version of the Queen Square criteria for iCAA were included. Baseline and follow-up MRIs were centrally analysed for markers of CAA using validated rating scales.

Results: We included 51 patients (68.6% male, median age at presentation 48 years), 51.0% with probable and 49.0% with possible iCAA. We evaluated 219 MRIs acquired over a median follow-up time of 3.7 years (IQR 1.8-6.4). There were 43 symptomatic intracerebral haemorrhages in 24 patients during follow-up, a rate of 16.7 per 100 patient-years.

Patients with previous supratentorial brain surgery had an ipsilateral-dominant distribution and spread of haemorrhagic markers on MRI. 14/51 (27.5%) patients had transient inflammatory changes (cortical or parenchymal oedema, sulcal hyperintensities). Haemorrhagic markers progressed during follow-up. In addition to 43 symptomatic ICH, 36 asymptomatic ICH (mostly smaller intragyral haemorrhages) were detected on follow-up scans. Besides numerous lobar microbleeds (median 16 at baseline, 53 at last follow-up), deep microbleeds were present in 19.6% of patients at baseline and 44.4% at follow-up. Severe perivascular spaces in centrum semiovale were common at baseline (64.7%) and follow-up (95.6%).

Conclusions: Patients with iCAA appear to have distinctive MRI characteristics, which might differentiate iCAA from other CAA subtypes and provide new insights into underlying disease mechanisms.

Key messages

What is already known on this topic

Iatrogenic cerebral amyloid angiopathy is a recently described disease, presumed to be caused by transmission of amyloid-ß pathology by medical procedures. Although clinical characteristics have been reported in several, often small, case series, there has been no systematic detailed characterisation of clinical and neuroimaging findings over time (including prognosis for future intracranial haemorrhage).

What this study adds

In this, the largest study on iatrogenic cerebral amyloid angiopathy to date that includes detailed baseline and follow-up neuroimaging, we report several distinctive findings including frequent deep cerebral microbleeds, inflammatory changes, high rates of both symptomatic and asymptomatic (mainly intragyral) intracerebral haemorrhage, and a tendency for lateralisation of haemorrhagic markers corresponding with the anatomical location of presumed amyloid-ß inoculation.

How this study might affect research, practice or policy

While iatrogenic cerebral amyloid angiopathy shares many clinical and neuroimaging findings with sporadic cerebral amyloid angiopathy, we describe several distinct neuroimaging observations, which could be helpful in differentiating between iatrogenic and sporadic cases, and provide new insights into underlying mechanisms of iatrogenic disease.

Background

An iatrogenic form of cerebral amyloid angiopathy (iCAA) is an increasingly recognized disease entity caused by the transmission of pathological amyloid-ß, most often by neurosurgical procedures using cadaveric dura, with other types of potential exposures also reported.[1–4] Most identified patients present with clinical and neuroimaging findings typical of sporadic cerebral amyloid angiopathy (CAA) but at an earlier age (i.e., below 50 years), with a history of prior (often childhood) neurosurgery or other medical procedures, and presentation with CAA occurring after a latency of decades. Diagnosis requires the exclusion of relevant genetic mutations, and confirmation of amyloid-ß deposition using amyloid-PET, cerebrospinal fluid analysis and/or biopsy.[4–7] The proposed Queen Square diagnostic criteria for iCAA provide a framework for identifying and investigating patients with possible or possible iCAA in clinical settings.[4]

However, many important questions and uncertainties remain. It remains unclear whether iCAA has a different phenotype or natural history to sporadic CAA in terms of clinical presentation, neuroimaging findings, or prognosis. Distinct neuroimaging markers in iCAA would be helpful for diagnosis, particularly in patients where the history of prior exposure is unclear, or in those presenting at an older age with a relevant prior exposure, in whom differentiation from sporadic CAA is currently challenging. Moreover, a better understanding of the clinical and neuroimaging phenotypes of iCAA could provide new insights into the underlying pathophysiological processes of iCAA, with potential relevance for the much more common sporadic CAA.

Therefore, we investigated the clinical-radiological presentation and natural history (including MRI neuroimaging phenotypes, their longitudinal changes, and clinical prognosis of iCAA) in a pooled analysis of individual patients included in a large, international multicentre cohort study.

Methods

We pooled individual patient data from previously reported studies describing clinical-radiological presentation and outcomes in patients with iCAA. We did a systematic search of published case series of ≥5 patients with iCAA on December 31st, 2023. We contacted lead authors from the three largest identified cohorts[4,6,7] who all agreed to participate in this multicentre study.

To be included in this study, patients needed to meet modified Queen Square criteria **(table 1)** for probable or possible iCAA[4] and have cerebral MRI at least at one timepoint. The Queen Square criteria were modified in the following ways: (1) to include patients with radiological features of CAA in the absence of a classical clinical syndrome for CAA, providing the patient had a relevant prior medical procedure (the original criteria required both typical clinical *and* radiological features of CAA), and (2) to explicitly acknowledge that the presence of deep cerebral microbleeds does not preclude the diagnosis of iCAA. In addition to previously published cases, we also included patients subsequently identified by the centres we approached.

Patient data were collected at the respective centres using a standardised case report form and included demographical data, information on presumed exposure, clinical symptoms, iCAA work-up and longitudinal follow-up data. Follow-up was individualised and at the clinical discretion of the treating team; usually this was annual in-person outpatient follow-up including MRI, but methods and intervals varied among participating sites. Follow-up outcome events of interest were: intracerebral haemorrhage (ICH); convexity subarachnoid haemorrhage (cSAH); seizures or new diagnosis of epilepsy; and death.

All MRIs were rated by a neurovascular specialist (SFH) with supervision by a senior neuroradiologist (DM), with case discussions in case of uncertainty. MRI protocols included susceptibility-weighted, T2-weighted, T2-weighted fluid attenuated inversion recovery, T1-

weighted and diffusion-weighted imaging in all patients. Post-gadolinium T1-weighted imaging was acquired where clinically indicated, at the discretion of the treating clinician. For inclusion in this study, patients needed to have at least one MRI scan; all available baseline and follow-up MRI scans were reviewed.

MRI scans were reviewed for the following markers of cerebral small vessel disease[8]: cerebral microbleeds (CMB) according to the Microbleed Anatomical Rating Scale (MARS)[9]; presence and distribution (focal or disseminated) of cortical superficial siderosis (cSS); white matter hyperintensities (WMH) severity according to the Fazekas scale[10] (severe defined as Fazekas scores of 2-3 in the deep white matter or Fazekas score of 3 for periventricular WMH)[11], as well as presence of a WMH multispot pattern[12]; enlarged perivascular spaces according to a validated four-point scale (severe defined as >20 visible perivascular spaces in one hemisphere)[13]; and the presence and number of lacunes. Acute haemorrhages (ICH, cSAH), previous ICH, previous ischaemic infarcts, diffusion-weighted imaging changes, cortical oedema and hyperintensities (as defined in the Barkhof ARIA scale[14]) and pathological intracranial contrast enhancement were also assessed.

We also assessed the lateralisation of haemorrhagic CAA markers in patients where unilateral supratentorial brain surgery was the likely inoculation (exposure) event, by calculating the ratio of ipsilateral to contralateral lobar CMBs, cSS and ICH. Ratios of ≥1.5 were defined as ipsilateral-dominant spread, while ratios <0.67 were defined as contralateral-dominant spread; intermediate ratios (0.68 to 1.49) were defined as neutral.

This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Statistical analysis

We performed statistical analysis using IBM SPSS Statistics for Windows, version 29 (IBM Corp, Armonk, USA). We used descriptive statistics to present the main findings and calculated incidence rates of recurrent haemorrhagic events during the follow-up. We investigated associations of deep CMB with lobar CMB and hypertension. Wilcoxon Signed-Rank tests were utilized to compare haemorrhagic markers between ipsilateral and contralateral hemispheres, and one-sample binomial tests were used to investigate whether the prevalence of ipsilateral and contralateral-dominant spread of haemorrhagic markers of CAA are similar. The Bonferroni correction was used to adjust for multiple comparisons to maintain a family-wise Type 1 error of $p < 0.05$. Uncorrected p-values are provided when tests met the adjusted criteria.

Ethical approvals

The study was approved by the ethics committee of the Medical University of Graz. Included patients either gave written informed consent or had consent waived for the use of retrospective data based on local ethics committee approvals at participating centres.

Results

Study cohort characteristics

We included 51 patients (68.6% male) of whom 26 patients (51.0%) met criteria for probable iCAA, 25 patients (49.0%) for possible iCAA (**table 2**). Baseline data for 39 of those patients have been reported previously (**Supplementary Table 1**).[4–7,15] The median age at exposure (i.e. potentially relevant medical procedure) was 9 years (IQR 2-21 years). The prior medical procedures included: cranial neurosurgery (n=36, 70.6%); spinal neurosurgery (n=11, 21.6%) and vascular embolization of the head and neck (n=4, 7.8%). The most frequent underlying medical conditions were: CNS tumours (37.3%); traumatic brain injury (31.4%); and congenital central nervous anomalies (spina bifida, cranio-stenosis, encephalocele, 15.7%). In 26 patients

(51.0%), the use of lyophilized cadaveric dura was confirmed in surgical notes; in five patients (9.8%) a dural patch of unknown type was used; and in 20 patients (39.2%), the original surgical notes could not be obtained. 14 patients (27.5%) had hypertension.

The median latency from exposure to presentation was 38 years (IQR 34-41 years), and the median age of first presentation with clinical symptoms was 48 years (IQR 41-59 years). An acute stroke syndrome due to ICH was the first clinical manifestation in 23 patients (45.1%); 18 patients had transient focal neurological episodes (with underlying cSAH) (35.3%); 4 had seizures (7.8%); 3 had cognitive decline (5.9%); and 3 patients presented with other, non-specific neurological symptoms (headache, diplopia, 5.9%). No associations were found between the latency to presentation and the clinical syndrome/event (p=0.98). 76.5% of patients had genetic testing and 52.9% of patients had evidence of CNS Aβ pathology by one or more modalities (45.1% by PET, 29.4% by CSF, 13.7% by biopsy, **table 2**).

Baseline MRI

Haemorrhagic markers of CAA were frequent: 48 (94.1%) had CMB, with a median of 18 CMB (IQR 6-45, **table 3**). Most CMB were lobar, but 10 patients (19.6%) also had deep CMB. 35 patients (68.6%) had cSS, of which 24 (47.1%) had disseminated cSS (≥4 sulci). While more than 20 enlarged perivascular spaces (grade 3 or above) in the centrum semiovale were found in the majority of patients (64.7%), severe WMH and WMH in a multispot pattern were less common (19.6% and 11.8%), as were enlarged perivascular spaces in the basal ganglia (Grade ≥3 in 2.0%). At baseline, all patients met Boston 2.0 neuroimaging criteria for probable CAA, with the exception of the 10 patients with deep CMBs.

Follow up and longitudinal MRI

Over a median follow-up time of 3.7 years (IQR 1.8 to 6.4 years, total 258 patient-years), there were 43 symptomatic recurrent ICH in 33 individual patients (64.7% of the study population),

and 15 recurrent cSAH in 14 individual patients (27.5%). The recurrence rate for ICH was 16.7 per 100 patient-years (95% CI: 12.7-21.9), and for cSAH was 5.8 per 100 patient-years (95% CI 3.6-9.9). One patient died during the observation period, following multiple recurrent ICH (**table 2**).

We evaluated 219 MRIs (51 baseline and 168 follow-up scans), with two or more longitudinal MRIs available in 45 patients (88.2%). In those patients, the median time between first and last available MRI was 3 years (IQR 1.6-4.7 years). In that time period, the group median for CMB number rose from 16 to 55, the number of patients with ≥50 lobar CMB from 22.2% to 51.1% and the proportion of patients with deep CMB increased to 44.4% (**table 3**). On further review of imaging for patients with deep CMB (**supplementary table 2**), we found that all had at least 10 lobar CMB, and had a higher number of lobar CMB than those without deep CMBs (median 60 vs 24). Most patients with deep CMB had disseminated cortical superficial siderosis (77.3%) and severe (Grade ≥3) enlarged perivascular spaces in the centrum semiovale (95.4%). Features suggestive of arteriolosclerosis (deep perforator arteriopathy), such as lacunes (13.6% vs 13.7%) and enlarged perivascular spaces in the basal ganglia (Grade ≥2 in 27.3% vs 27.6%), were equally frequent in patients with and without deep CMB. Other structural imaging markers of cerebral small vessel disease were similar in patients with and without deep CMB. The presence of deep CMB was not associated with hypertension or age. In addition to deep CMB, three patients had macrohaemorrhages in deep locations; example imaging from two patients with deep haemorrhagic lesions are shown in **figure 1**.

cSS was found in 89% of patients at time of last follow-up, with disseminated cSS in 73%. At last follow-up almost all patients had severe perivascular spaces in the centrum semiovale (96%), but lower proportions had severe WMH (33%), a WMH multispot pattern (20%), or severely enlarged perivascular spaces in the basal ganglia (4%). **Figure 2** depicts an example of progression of iCAA over a three-year period.[16]

Other imaging features

(1) Laterality of CAA neuroimaging markers

In the 23 patients with unilateral supratentorial brain surgery as the source of exposure, we observed focal patterns of haemorrhagic markers of CAA at baseline and follow-up (**table S3**). On baseline imaging, patients had a greater number of CMB within the ipsilateral versus the contralateral hemisphere (median 10 [IQR 4-19] vs. 5 [IQR 1-11]); there was a tendency towards cSS involving ipsilateral sulci rather than contralateral sulci (median 2 [IQR 0-6] vs. 1 [IQR 0-4]); and more ipsilateral ICH (median 1 [IQR 0-1] vs. median 0 [IQR 0-1, total sum 21 vs. 13**)**. Similar patterns were seen at final available follow-up for ipsilateral CMB (median 26 [IQR 11-55] vs. 9 [5-35]) and ipsilateral sulci affected by cSS (median 6 [IQR 3-9] vs. median 3 [IQR 0-10]); but not for ipsilateral ICH (median 1 [IQR 1-3] vs. median 1 [IQR 0-2], total sum 38 vs. 31). **Figure 3** visualises differences in the distribution of CMB between the ipsilateral and contralateral hemispheres at baseline and last follow-up.

On baseline imaging, 14 patients (60.9%) had ipsilateral dominance of CMB (ratios ≥1.5) whereas only 5 patients (21.7%) had contralateral CMB dominance (ratios <0.67). When considering cSS (present in 17 patients), 9 patients (52.9%) had ipsilateral dominant cSS compared to 4 patients (23.5%) with contralateral dominance. Similar observations were made for ICH (present in 18 patients, counting both acute and chronic haemorrhages), with 13 patients (72.2%) showing a majority of ipsilateral ICH (ratio of ≥1.5, including only unilateral presence) compared to 3 patients (16.7%) with contralateral majority at baseline. We found stronger evidence for ipsilateral-dominant disease on the last available follow-up MRI (ipsilateral versus contralateral patterns of CMB in 65.2% vs. 8.7%, p=0.002; for cSS, 73.7% vs. 5.3%, p<0.001; for ICH, 55.0% vs. 15.0% **table S3**). By contrast, no focal patterns of non-haemorrhagic markers at baseline or follow-up were found. In patients with infratentorial or spinal surgery,

no patterns of lateralisation were found (left-sided dominance of CMB in 17.9%, right-sided dominance in 10.7%, similar distribution in 71.4% of patients at last follow-up).

Two examples of patients with such focal ipsilateral evolution patterns are depicted in **figure 4**.

(2) Neuroimaging findings suggesting inflammation

Cortical oedema, parenchymal and sulcal hyperintensities, suggesting inflammation, were found in 14 patients (27.4%) at any time point. These abnormalities were usually an incidental finding on MRI and fully resolved on follow-up scans. 12/14 patients showed cortical oedema, 8/14 sulcal hyperintensities and 5/14 parenchymal hyperintensities. In most patients (10/14), a single lobe was affected. Two examples of transient inflammatory changes in iCAA are shown in **figure 5**. There were no differences in the severity of CMB or CSS progression between patients with and without inflammatory changes ($p>0.2$).

(3) Asymptomatic ICH

In addition to the high rates of symptomatic ICH and cSAH recurrence, we observed a high number of apparently asymptomatic ICH (defined as ICH incidentally found on neuroimaging without associated documented clinical symptoms). At baseline MRI, a total of 64 ICH were visible (in contrast to only 23 recorded symptomatic ICH). During the follow-up period, 79 additional ICH were found, of which 33 were smaller intragyral haemorrhages (while only 43 ICH were recorded clinically). The median number of ICH per patient rose from 1 (IQR 0-2) to 2 (IQR 1-4).

Discussion

In this international multicentre clinical-radiological cohort study investigating the clinical and neuroimaging findings of patients with iCAA, we found several aspects of interest. First, we observed a marked progression in haemorrhagic markers of CAA (including CMBs, cSS, and ICH) over the median MRI follow-up time of 3 years, suggesting an active haemorrhage-prone vasculopathic disease phase after a long latent period following presumed exposure (inoculation). Besides a large number of symptomatic ICH, many patients showed asymptomatic smaller (frequently intragyral) ICH. Haemorrhagic lesions were also frequently detected in deep brain areas, which are not permitted in the diagnostic criteria for 'sporadic' CAA. Second, we found evidence for lateralised progression of these haemorrhagic CAA markers in a subset of patients, which might have pathophysiological relevance. Thirdly, we found that asymptomatic findings suggestive of transient inflammation were common, which might imply a role for inflammation in the pathophysiology of iCAA.

The longitudinal analysis of both clinical and neuroimaging data provides new data on the clinical trajectory of iCAA. During the follow-up period, we found high rates of both symptomatic and asymptomatic haemorrhages, with almost half of the patients having an at least one symptomatic (recurrent) ICH, and the median number of CMB increasing more than three-fold. Despite the high ICH rate, the mortality rate was surprisingly low. This could be explained by smaller haemorrhages, precise detection of haemorrhages during frequent follow-ups, selection bias (failure to diagnose diagnosis iCAA in patients with a fatal index ICH) and higher survival rates in a younger population compared to general ICH cohorts, who might have more comorbidities and less functional reserve. We also found that more than 40% of patients had deep haemorrhagic lesions (CMBs). Amyloid-ß deposition in CAA is usually considered to occur almost exclusively in the leptomeningeal and cortical arteries and arterioles[17]; however, neuropathological studies show that in severe stages, CAA can affect deep structures, particularly the deep grey nuclei (which include the thalamus and basal ganglia).[18] Previous iterations of the MRI-based Boston criteria for CAA require an absence of alternative

diagnoses; for patients with sporadic CAA, the most common of these is arteriolosclerosis, which is characterised by haemorrhages in deep structures. The most recent version of the Boston criteria explicitly excludes those with deep haemorrhagic features from having a CAA diagnosis, and deep haemorrhages are not found in patients with Dutch-type hereditary CAA, an inherited form of amyloid-beta CAA.[20] In our iatrogenic cohort, coexisting arteriolosclerosis is less a plausible explanation for deep haemorrhagic changes, given their age (younger) and relative absence of coexisting vascular risk factors such as hypertension. It therefore seems most likely that these deep haemorrhagic changes, also reported in previously published cases of iatrogenic CAA[4], are CAA-related, representing either a high degree of CAA severity or a unique neuroimaging feature of iatrogenic disease (e.g. due to regional vulnerability to amyloid-ß prions). There are post-mortem reports demonstrating amyloid-ß deposition in the basal ganglia and thalamus in iatrogenic cases, supporting this view.[1] Whilst iatrogenic CAA shares many features with sporadic and inherited CAA, it will not necessarily be identical to these disease forms; one recognised difference is age of onset. The rapid progression of haemorrhagic markers and the large number of (both symptomatic and smaller intragyral) intracerebral haemorrhages suggest an active haemorrhage-prone vasculopathy in iatrogenic CAA. Similar well-recognised clinical and radiological differences are observed between acquired (iatrogenic and variant) and sporadic forms of Creutzfeldt-Jakob Disease (CJD).[19]

In most patients where exposure to amyloid-ß was unilateral and supratentorial, we found a lateralised spread of haemorrhagic lesions, with ICH, CMB and CSS found predominantly in the ipsilateral hemisphere. This extends the findings from a recent meta-analysis of 24 previously reported patients with iCAA, which also showed a larger rate of ICH ipsilateral to the site of suspected amyloid-ß transmission, although this study was limited by the retrospective inclusion of case reports.[21] The lateralisation of these haemorrhages suggests a locally active pathophysiological process at later disease stages. Prions have “two-stage

kinetics", with distinct periods of firstly propagation (exponential increase in prion titre) and then toxicity (where cell death occurs)[22]; if amyloid-ß behaves similarly, a model for which there is some supporting experimental data,[23] then the vasculopathy and subsequent haemorrhages observed would occur during the later toxicity stage. The reasons for selective vulnerability to toxicity near the site of presumed inoculation in those who underwent supratentorial brain surgery are not known, but lateralisation of Aβ pathology after intracerebral inoculation has been observed in animal models of Aβ transmission.[24] This is particularly perplexing as, for example in patients with iatrogenic CAA following spinal surgery, there is evidence of vascular toxicity at sites far removed from the presumed site of inoculation, supporting the argument that there is widespread propagation of Aβ following exposure. The further exploration of these hypotheses in experimental models will have relevance to iatrogenic and other forms of CAA.

Another finding frequently detected in patients with iCAA was of MRI findings suggesting inflammation. While such changes are sometimes seen in CAA-related inflammation or as amyloid-related imaging abnormalities (ARIA) in immunotherapy trials for Alzheimer's disease, the proportion in iatrogenic CAA (nearly 1 in 3) is higher than reported rates in patients with sporadic CAA. It is tempting to speculate that these inflammatory changes might reflect focal attempts to clear this exogenously introduced amyloid-ß peptide; similar to amyloid-related imaging abnormalities, these findings appeared to be mostly asymptomatic.[25]

We found a high frequency of enlarged perivascular spaces in the centrum semiovale in the majority of patients (in almost all patients at the last follow-up), but rather mild and non-specific white matter hyperintensities in most patients. This might reflect the younger age of patients with iCAA (compared to sporadic CAA and other age-related neurodegenerative disorders leading to WMH) but also underlines the potential relevance of enlarged perivascular spaces

(and perhaps impaired perivascular clearance of amyloid-ß) in the diagnosis and pathophysiology of iCAA as well as sporadic CAA.[26,27]

The core strength of this study is the utilisation of longitudinal neuroimaging and clinical data in the largest multicentre cohort of patients with iCAA assembled to date, with the central consistent analysis of scans by a single observer helping in the consistent identification of neuroimaging patterns specific to iCAA. Our modified Queen Square Criteria are provided in **table 1**, together with clarification that deep haemorrhagic markers should not prevent a diagnosis of iCAA. However, as iCAA is a rare disease, the number of included patients is still modest, and selection bias towards patients who are younger and have a more aggressive phenotype (a group more likely to come to medical attention and be referred to expert centres) is probable. Additionally, imaging protocols and follow-ups varied between centres, and again may be prone to detection bias towards more severe disease (i.e. those with frequent clinical presentations), although in our cohort routine MRI follow-up was performed regularly by all participating centres and not only driven by clinical symptoms, mitigating this risk. All patients were assessed by a single rater with further expert supervision, but interrater reliability assessment was not performed and blinding to diagnoses and hypothesis was not possible in our study setting. Statistical comparisons are limited due to the modest study size, particularly regarding the analysis of the focal spread of haemorrhagic markers. Therefore, validation of these findings in future studies would be important.

In conclusion, our findings seem to show a specific neuroimaging profile of iCAA – including rapid and aggressive progression of haemorrhagic changes after presentation (i.e., in the symptomatic phase of disease), focal ipsilateral spread of haemorrhagic markers, deep CMB, frequent inflammatory changes and a large number of frequently asymptomatic intragyral ICH. These results may have implications in the diagnosis but also provide new insights into the

pathophysiology of iCAA, which appears to be a distinct subtype with its own characteristic neuroimaging and clinic natural history.

Table 1: Modified Queen Square criteria for iatrogenic cerebral amyloid angiopathy

Diagnostic criterion		Probable	Possible
Age of onset	**<55 years**	x	x
	≥55 years		x
History of potential exposure (one or more) • Procedure/treatment using cadaveric human CNS tissues • Relevant neurosurgical procedure (brain, spinal cord, posterior eye)		x	x
Clinical and/or radiological features of CAA • Clinical presentation, at least one of: o spontaneous intracerebral haemorrhage (associated with an appropriate clinical syndrome, e.g., symptoms of acute stroke, focal or generalised seizures) o convexity subarachnoid haemorrhage (associated with an appropriate clinical syndrome, e.g., transient focal neurological episodes) o cognitive impairment		x	
• Radiological features, at least one of: o intracerebral haemorrhage (at least one lobar; deep haemorrhage does not exclude iCAA) o convexity subarachnoid haemorrhage o cerebral microbleeds (predominantly lobar; deep cerebral microbleeds do not exclude iCAA) o cortical superficial siderosis		x	x
Evidence of Aβ accumulation in the CNS (one or more) • Positive amyloid PET-scan • Supportive cerebrospinal fluid Aβ profile • Brain biopsy demonstrating vascular Aβ -deposition		x	
Exclusion of genetic causes of Aβ-CNS disease • APP mutations including copy number variants, *PSEN1*, *PSEN2* • In those without evidence of CNS Aβ accumulation next-generation sequencing for non-Aβ CAA mutations		x	

Table 2: Clinical characteristics of the study cohort at baseline (n=51)

	All patients (n=51)	Probable iCAA (n=26)	Possible iCAA (n=25)
Demographical data			
Male sex (n, %)	35 (68.6%)	20 (76.9%)	15 (60.0%)
Age at exposure in years (median, IQR)	9 (2-21)	9 (1-19)	12 (2-28)
Exposure event type			
Cranial surgery (n, %)	36 (70.6%)	18 (69.2%)	18 (72.0%)
Spinal surgery (n, %)	11 (21.6%)	5 (19.2%)	6 (24.0%)
Head and neck embolization (n, %)	4 (7.8%)	3 (11.5%)	1 (4.0%)
Usage of cadaveric dura			
Confirmed lyophilized dura usage (n, %)	26 (51.0%)	14 (53.8%)	12 (48.0%)
Dura patch of unknown type (n, %)	5 (9.8%)	4 (15.4%)	1 (4.0%)
Missing information on usage (n, %)	20 (39.2%)	8 (30.8%)	12 (48.0%)
Symptomatic presentation			
Intracerebral haemorrhage (n, %)	23 (45.1%)	10 (38.5%)	13 (52.0%)
Convexity subarachnoid haemorrhage/ transient focal neurological episode (n, %)	18 (35.3%)	11 (42.3%)	7 (28.0%)
Seizures	4 (7.8%)	4 (15.4%)	0
Cognitive decline (n, %)	3 (5.9%)	1 (3.8%)	2 (8.0%)
Incidental diagnosis (n, %)	3 (5.9%)	0	3 (12.0%)
Latency from exposure, time in years (median, IQR)	38 (34-41)	37 (34-40)	40 (35-41)
Age at symptom onset, years (median, IQR)	48 (41-59)	46 (40-54)	52 (44-63)
Arterial hypertension	14 (27.5%)	9 (34.6%)	5 (20.0%)
CAA adjunct investigations			
Genetic testing performed* (n, %)	39 (76.5%)	26 (100%)	13 (52.0%)
Amyloid positron emission tomography indicating amyloid-ß deposition (n, %)	23 (45.1%)	23 (88.5%)	0
Cerebrospinal fluid analysis indicating amyloid-ß pathology (n, %)	15 (29.4%)	15 (29.4%)	0
Histopathological confirmation of CAA (n, %)	7 (13.7%)	6 (23.1%)	1 (4.0%)
Follow-up events			
Clinical follow-up duration in years (median, IQR)	3.7 (1.8-6.4)	5.3 (2.8-7.8)	2.6 (1.6-5.1)
Intracerebral haemorrhage (n, %)	33 (64.7%)	17 (65.4%)	16 (64.0%)
Convexity subarachnoid haemorrhage (n, %)	14 (27.5%)	8 (30.8%)	6 (24.0%)
Mortality (n, %)	1 (2.0%)	1 (3.8%)	0

**Genetic testing included at least the exclusion of duplications in APP and mutations in APP, PSEN1 and PSEN2.*

Table 3: MRI findings over time

	Baseline MRI (full cohort) n=51	**Baseline MRI (patients with MRI FU), n=45**	**Last MRI (patients with MRI FU), n=45**
Microbleeds, any	48 (94.1%)	42 (93.3%)	45 (100%)
Microbleed number (median, IQR)	18 (6-45)	16 (4-38)	55 (20-111)
Lobar microbleed number (median, IQR)	16 (5-40)	14 (3-38)	53 (18-109)
≥10 lobar microbleeds	31 (60.8%)	26 (57.8%)	43 (95.6%)
≥50 lobar microbleeds	11 (21.6%)	10 (22.2%)	23 (51.1%)
Deep microbleeds, any	10 (19.6%)	8 (17.8%)	20 (44.4%)
Cortical superficial siderosis, any	35 (68.6%)	29 (64.4%)	40 (88.9%)
Disseminated cortical superficial siderosis	24 (47.1%)	19 (42.2%)	33 (73.3%)
Macrohaemorrhages (median, IQR)	1 (0-1)	1 (0-1.5)	2 (0-3)
Macro- and intragryral haemorrhages (median, IQR)	1 (0-2)	1 (0-2)	2 (1-4)
Deep white matter hyperintensities			
Fazekas Scale: 0	11 (21.6%)	11 (24.4%)	3 (6.7%)
Fazekas Scale: 1	32 (62.7%)	27 (60.0%)	28 (62.2%)
Fazekas Scale: 2	5 (9.8%)	4 (8.9%)	8 (17.8%)
Fazekas Scale: 3	3 (5.9%)	3 (6.7%)	6 (13.3%)
Periventricular white matter hyperintensities			
Fazekas Scale: 0	7 (13.7%)	5 (11.1%)	1 (2.2%)
Fazekas Scale: 1	27 (52.9%)	25 (55.6%)	18 (40.0%)
Fazekas Scale: 2	11 (21.6%)	9 (20.0%)	16 (35.6%)
Fazekas Scale: 3	6 (11.8%)	6 (13.3%)	10 (22.2%)
Severe white matter hyperintensities	10 (19.6%)	9 (20.0%)	15 (33.3%)
White matter hyperintensity multispot pattern	6 (11.8%)	6 (13.3%)	9 (20.0%)
Lacunes, any	4 (7.8%)	4 (8.9%)	7 (15.6%)
Enlarged perivascular spaces (centrum semiovale)			
Grade 0 (0)	0	0	0
Grade 1 (1-10)	1 (2.0%)	1 (2.2%)	0
Grade 2 (11-20)	17 (33.3%)	17 (37.8%)	2 (4.4%)
Grade 3 (21-40)	24 (47.1%)	19 (42.2%)	24 (53.3%)
Grade 4 (>40**)**	9 (17.6%)	8 (17.8%)	19 (42.2%)
Enlarged perivascular spaces (basal ganglia)			
Grade 0 (0)	3 (5.9%)	3 (6.7%)	0
Grade 1 (1-10)	39 (76.5%)	34 (75.6%)	32 (71.1%)
Grade 2 (11-20)	8 (15.7%)	7 (15.6%)	11 (24.4%)
Grade 3 (21-40)	0	0	1 (2.2%)
Grade 4 (>40**)**	1 (2.0%)	1 (2.2%)	1 (2.2%)

Declarations

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Figure 1: Patients with iatrogenic cerebral amyloid angiopathy and deep haemorrhagic lesions

Legend, A: *Patient with cerebral amyloid angiopathy diagnosed in their forties, with a history of craniosynostosis and brain surgery as an infant with use of lyophilised dura. In addition to severe CAA-related changes including disseminated superficial siderosis and lobar microbleeds (A2), MRI shows three deep (thalamic) microbleeds and evidence of a previous larger thalamic haemorrhage (A1). No other imaging markers of arteriolosclerosis (such as lacunes or enlarged perivascular spaces in the basal ganglia) were found in this patient (A3/A4). The patient had mild and well-controlled arterial hypertension; amyloid deposition confirmed using Amyloid PET and cerebrospinal fluid analysis (marked reduction of both amyloid-beta40 and amyloid-beta42); genetic testing identified no variants associated with hereditary CAA.*

B: *Patient in their forties with a history of craniectomy following a traumatic brain injury in early childhood, with recorded usage of a dural patch. In addition to an acute right frontal ICH, their MRI shows disseminated superficial siderosis and lobar microbleeds (B2), as well as a single microbleed in the left thalamus (B2). No other imaging markers of arteriolosclerosis were found in this patient (B3/B4), who had no history of hypertension. Amyloid PET was positive for amyloid deposition, and genetic testing for variants associated with hereditary CAA was negative.*

Figure 2: Neuroimaging example of progression of iatrogenic cerebral amyloid angiopathy

Legend: *Patient in their forties with history of occipital craniectomy with use of lyophilized cadaveric dura after traumatic brain injury in childhood. The patient first presented with a small left-sided occipital intracerebral haemorrhage (A1), MRI showed early confluent white matter hyperintensities (A2) and some lobar microbleeds (A3) near the occipital craniotomy, with no microbleeds identified elsewhere (A4/5). Two years later, the patient presented with a large right frontoparietal intracerebral haemorrhage (B1). While white matter hyperintensities showed only mild progression three years after the index presentation (B2), there was extensive progression of lobar microbleeds, with new cortical superficial siderosis and multiple small intragyral haemorrhages (B3-B5).*

Figure 3: Distribution of cerebral microbleeds (CMB) between the ipsilateral and contralateral sides of likely exposure (inoculation) with amyloid-ß at baseline and last follow-up

Legend: Each numbered bar represents an individual patient. CMB = cerebral microbleed.

Figure 4: Neuroimaging examples of ipsilateral spread of haemorrhagic neuroimaging findings in patients with iatrogenic cerebral amyloid angiopathy

Legend, A: *Patient in their sixties with history of left parietal haematoma evacuation (A1) with usage of a dural patch (further details not known), following a traumatic brain injury in early adulthood. MRI at baseline showed small intragyral haemorrhages and lobar microbleeds in the left parietal and occipital lobes (A2). Two years later, haemorrhagic markers had progressed, particularly in the left hemisphere (A3-A5).*

B: *Patient in their forties with history of left frontoparietal haematoma evacuation (B1) with use of a lyophilized cadaveric dura patch, after traumatic brain injury sustained in early childhood. The patient presented with an acute left frontal intracerebral haemorrhage (B2), additionally showing a small intragyral haemorrhage in the left parietal lobe (B2), and a few cerebral microbleeds restricted to the left parietal and temporal lobes (B3). At final available follow-up (four years later), the haemorrhagic markers had progressed further, with cerebral microbleeds, cortical superficial siderosis and intragyral haemorrhages mainly in the left hemisphere (B4/B5).*

Figure 5: Neuroimaging examples of MRI findings suggesting inflammation in patients with iatrogenic cerebral amyloid angiopathy

Legend, A: *Patient diagnosed with cerebral amyloid angiopathy in their forties, with a history of craniocervical dermoid cyst removal with use of lyophilised dura in early childhood. On a routine follow-up scan three years after CAA presentation, there were patchy cortico-subcortical T2/FLAIR hyperintensities in the right parietal lobe (A1/A2) associated with leptomeningeal enhancement (A3). Three months later, these T2-hyperintensities had mostly disappeared (A4) and the leptomeningeal enhancement had resolved (A5).*

B: *Patient in their forties presenting with seizures, who had a choroid plexus papilloma resection with use of a dural patch in childhood. MRI showed left frontal cortical hyperintensity and swelling (B1). A follow-up scan 5 weeks later showed progression of the cortical changes (B2) as well as leptomeningeal enhancement (B3). After treatment with corticosteroids, the cortical swelling and hyperintensity resolved (B4) and the leptomeningeal enhancement regressed (B5).*