IATROGENIC CEREBRAL AMYLOID ANGIOPATHY: AN EMERGING CLINICAL PHENOMENON

Gargi Banerjee MRCP PhD[1], Kiran Samra MRCP[2], Matthew E Adams FRCR[3], Zane Jaunmuktane FRCPath[4,5], Adrian R Parry-Jones PhD[6,7], Joan Grieve FRCS MD[8], Ahmed K Toma FRCS MD[8], Simon F Farmer PhD[9], Richard Sylvester PhD[9], Henry Houlden PhD[4], Peter Rudge FRCP[1], Simon Mead PhD[1], Sebastian Brandner MD FRCPath[1,2,5], Jonathan M Schott MD[2], John Collinge FRCP DSc[1], David J Werring FRCP PhD[10]

[1]MRC Prion Unit at UCL, Institute of Prion Diseases, Courtauld Building, London, UK.

[2]Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK

[3]Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK.

[4]Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK.

[5]Division of Neuropathology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK.

[6]Division of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

[7]Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, UK.

[8]Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK.

[9]Department of Neurology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London, UK.

[10]Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK

Corresponding Author

Dr Gargi Banerjee

MRC Prion Unit at UCL, Institute of Prion Diseases,

Courtauld Building, 33 Cleveland Street,

London W1W 7FF

g.banerjee@ucl.ac.uk

Title:	71 characters
Abstract:	196 words
Word Count:	3771 words

(excluding title page, abstract, abbreviations, references, tables, figure legends)

Number of figures:	2
Number of tables:	3
Supplementary tables:	2

ABSTRACT

In the last six years following the first pathological description of presumed amyloid-beta (Aβ) transmission in humans (in 2015) and subsequent experimental confirmation (in 2018), clinical cases of iatrogenic cerebral amyloid angiopathy (CAA) – attributed to the transmission of Aβ seeds - have been increasingly recognised and reported. This newly described form of CAA is associated with early disease onset (typically in the third to fifth decade), and often presents with intracerebral haemorrhage (ICH) but also seizures and cognitive impairment. Although assumed to be rare, it is important that clinicians remain vigilant for potential cases, particularly as the optimal management, prognosis, true incidence, and public health implications remain unknown. This review summarises our current understanding of the clinical spectrum of iatrogenic CAA and provides a diagnostic framework for clinicians.

We provide clinical details for three patients with pathological evidence of iatrogenic CAA and present a summary of the published cases to date (n=20), identified following a systematic review. Our aims are: (1) to describe the clinical features of iatrogenic CAA, highlighting important similarities and differences between iatrogenic and sporadic CAA; and (2) to discuss potential approaches for investigation and diagnosis, including suggested diagnostic criteria for iatrogenic CAA.

KEY WORDS

Amyloid; cerebral amyloid angiopathy; iatrogenic; intracerebral haemorrhage; prion.

ABBREVIATIONS

ApoE	Apolipoprotein E
AVM	Arteriovenous malformation
CAA	Cerebral amyloid angiopathy
CSF	Cerebrospinal fluid
CT	Computed tomography
DSA	Digital subtraction angiography
ICH	Intracerebral haemorrhage
MRI	Magnetic resonance imaging
PET	Positron emission tomography

INTRODUCTION

In the six years following the first pathological description of presumed amyloid-beta (Aβ) transmission in humans[1] and subsequent experimental confirmation[2], clinical cases of iatrogenic cerebral amyloid angiopathy (CAA) – attributed to the transmission of Aβ seeds - have been increasingly recognised and reported. This newly described form of CAA is associated with early disease onset (typically in the third to fifth decade), and often presents with intracerebral haemorrhage (ICH) but also seizures and cognitive impairment. Although assumed to be rare, it is important that clinicians remain vigilant for potential cases, particularly as the optimal management, prognosis, true incidence, and public health implications remain unknown.

In this review, we describe the clinical features of three patients diagnosed with iatrogenic CAA whose pathological findings we have reported previously[3], and present a descriptive summary of the published cases with clinical details to date. Our aims are: (1) to review the clinical features of iatrogenic CAA; and (2) to discuss potential approaches for investigation and diagnosis, including suggested diagnostic criteria for iatrogenic CAA.

MATERIALS & METHODS

We searched PubMed (Medline) and EMBASE databases on June 17th 2021 for published cases of iatrogenic CAA.

The following search strategies were used:

- PubMed (Medline):

("cerebral amyloid angiopathy"[MeSH Terms] OR "vascular amyloidosis"[tw] OR (cerebral[tw] AND "amyloid angiopath*"[tw])) AND ("cadaver"[MeSH Terms] OR "cadaver*"[tw] OR "iatrogenic disease"[MeSH Terms] OR iatrogen*[tw] OR "prion diseases"[MeSH Terms] OR "prions"[MeSH Terms] OR prion*[tw] OR "dura mater"[MeSH Terms] OR dura[tw] OR dural[tw]

OR "growth hormone"[MeSH Terms] OR "growth hormone*"[tw] OR "neurosurgery"[MeSH Terms] OR "neurosurgical procedures"[MeSH Terms] OR neurosurg*[tw] OR "brain surg*"[tw] OR "spine surg*"[tw] OR "ophthalmologic surgical procedures"[MeSH Terms] OR "eye surg*"[tw] OR "age of onset"[MeSH Terms] OR early-onset[tw])

- EMBASE:

(exp vascular amyloidosis/ OR cerebral amyloid angiopathy.mp. OR cerebral adj4 amyloid angiopath*.mp.) AND [(exp cadaver/ OR cadaver*.mp.) OR (exp *iatrogenic disease/ OR iatrogen*.mp.) OR (exp *prion disease/ OR exp *prion/ OR prion*.mp.) OR (exp dura mater/ OR dura.mp. OR dural.mp.) OR (exp growth hormone/ OR growth hormone*.mp.) OR (exp "patient history of neurosurgery"/ OR exp neurosurgery/ OR exp brain surgery/ OR exp spine surgery/ OR exp eye surgery/ OR neurosurg*.mp.) OR (exp onset age/ OR early onset.mp.)]

Only reports in English were included. The reference lists for all selected papers were reviewed for further relevant cases. Cases with co-existing iatrogenic Creutzfeldt-Jakob disease (CJD) were excluded, as co-existence of this diagnosis would likely mask a clinical presentation of iatrogenic CAA, given the rapid progression and severity of neurological symptoms in iatrogenic CJD. Additionally, cases where there was no clear iatrogenic precipitant reported (i.e. a procedure involving the brain, spinal cord, or eyes, or one using human cadaveric material) were excluded. Figure 1 shows the PRISMA flowchart for record inclusion.

Pre-mortem diagnosis was defined as diagnosis made during life, based on clinical presentation, brain imaging and/or brain biopsy. Post-mortem diagnosis was defined as cases where the diagnosis was made after death.

CASE REPORTS

Case 1

A male in his late 30s presented with headache, left-sided retro-orbital pain, and a left homonymous hemianopia, and shortly afterwards developed left-sided weakness and became obtunded. Immediate CT imaging identified an acute right parieto-occipital intracerebral haemorrhage (Figure 2; panel a). He had been previously fit and well, and there was no family history of brain haemorrhage or cognitive impairment. The patient underwent an emergency craniotomy and haematoma evacuation; pathological evaluation (cerebral cortex and overlying arachnoid, in addition to haematoma) revealed cortical and leptomeningeal vessels with concentric Aβ deposition, in keeping with CAA, as well as small extravascular deposits of Aβ (but no typical plaques). There was prominent cortical hyper-phosphorylated tau pathology in the form of threads, occasional pre-tangles and neuritic plaques, but no glial tau pathology[3]. There was no evidence of TDP43 or alpha-synuclein pathology. MRI brain revealed multiple cortical and white matter microhaemorrhages, surrounding the area of macro-haemorrhage. ApoE genotype was ε2/ε3. Next generation sequencing (NGS) did not detect mutations in genes associated with dementia (see note, Supplementary Table 1, for details of genes tested); further testing did not identify duplication of the *APP* gene.

This patient's past medical history was notable for a congenital right-sided post-auricular arteriovenous malformation (AVM). In 1983, he had angiography and embolisation of this AVM (embolisation material not recorded); he had further embolisation procedures in 1984 (using lyophilised dura), 1987 and 1988 (using "Ivalon" polyvinyl alcohol particles), after which the AVM was surgically resected (1988).

Four months following initial presentation, he required ongoing neurorehabilitation for cognitive difficulties; by 18 months most of the deficits associated with his acute stroke had resolved, such that he was able to return to work full time, though he reported some difficulties

with multitasking. On clinical examination at the time of our review (10 months following initial presentation), he had a left homonymous hemianopia, left-sided hyperreflexia and hemisensory loss. He continued to demonstrate mild visuospatial under-functioning in the context of his visual field deficits, with attentional and working memory inefficiencies, reduced processing speed, and impaired verbal recall. Repeat MRI (Figure 2; panels b, c, d) at this stage demonstrated stable appearances of the microhaemorrhages, with interval resolution of the haematoma.

Case 2

A female in her mid-40s presented with four stereotyped episodes of left-sided sensory symptoms (paraesthesia, “coldness”) which spread over five minutes from her shoulder into her hand. Two of them occurred within a few days, and a further two over the next three months. The episodes were associated with weakness of the arm (and on one occasion, the face) and mild neck discomfort.

Her past medical history was notable for an expanding congenital haemangioma involving the right orbit. In 1980, she underwent embolisation of this haemangioma using lyophilised cadaveric dura mater; she had further embolisation and resections in 1981 (lyophilised dura) and 1982 (embolisation material not recorded), as well as postsurgical radiotherapy (1983). She was also known to have beta thalassaemia trait, and iron and vitamin D deficiencies. There was no family history of brain haemorrhage or cognitive impairment. At the time of her initial examination, there were longstanding sequelae from her previous surgeries (right superior quadrantanopia; right-sided ptosis; limited range of movement of the right eye in all directions of gaze; right-sided facial weakness); the remaining neurological examination was normal.

Her initial MRI brain (Figure 2; panels e, f) demonstrated a recent right-sided parieto-occipital convexity subarachnoid haemorrhage, as well as bilateral, multifocal regions of cortical

superficial siderosis and a small number of lobar microhaemorrhages. Interval imaging eight months later showed stable appearances, despite the occurrence of two further transient neurological episodes.

At the time of assessment by our service (14 months after her original presentation), there were no new clinical findings. MR imaging demonstrated further regions of superficial siderosis in both cerebral hemispheres (Figure 2). Neuropsychometry at this stage demonstrated mild-to-moderate non-verbal under-functioning and mild executive dysfunction, suggestive of mild anterior dysfunction. ApoE genotype was ε3/ε3. NGS did not detect mutations in genes associated with dementia (see note, Supplementary Table 1, for details of genes tested), but did identify a heterozygous variant of uncertain clinical significance in *NOTCH3* (c.2183 G>A p.; Arg728His). Further testing did not identify duplication of the *APP* gene.

Two weeks after our assessment, she was admitted locally with severe right-sided headache, left-sided weakness and paraesthesia, and slurred speech; unlike her previous episodes, this did not spontaneously resolve. Repeat imaging showed a large acute lobar haematoma in the frontal region and a smaller, separate acute haematoma in the precentral gyrus (Figure 2; panel h); the patient was urgently transferred to our centre for further evaluation. Digital subtraction angiography (DSA) did not demonstrate a macrovascular cause for her ICH. A diagnostic brain biopsy showed severe and widespread CAA involving the leptomeninges and cortex, as well as evidence of Alzheimer's disease-type pathology, namely frequent diffuse Aβ parenchymal plaques, and widespread tau pathology (including frequent pre-tangles, occasional tangles, and occasional neuritic plaques containing both Aβ and tau)[3]. She was discharged after a two week admission, and made good improvements in her left hand function in the months following this. Seven months later, she re-presented with sudden-onset dysphasia and reduced conscious level; CT revealed a new left frontal lobe ICH. Her hospital admission (lasting six months) was complicated by a traumatic left-sided subdural haemorrhage requiring a burr hole and surgical evacuation (approximately two months into

her admission), a further ICH (left frontal, near the surgical site, day one post-operatively), and generalised seizures (starting two weeks post-operatively). Approximately 6 months following her discharge, she had a further ICH and died shortly thereafter.

Case 3

A male in his mid-40s was admitted for investigation of rapidly progressive cognitive impairment, ataxia and myoclonus. Over a period of approximately 12 months, he developed distressing visual hallucinations, nonsensical confused speech, visuospatial disorientation in his own home and difficulty identifying familiar objects; he newly required prompting for basic tasks such as toileting. He additionally developed urinary urgency, faecal incontinence and gait unsteadiness.

The patient underwent resection of a posterior fossa medulloblastoma in 1976; it is unclear if dural grafting was performed. He had post-operative whole brain and spine radiotherapy, and two years later required a ventriculo-peritoneal shunt for hydrocephalus. He subsequently received treatment with recombinant (not cadaveric) growth hormone (1980s); he was noted to have mild learning difficulties, but otherwise made a full recovery. Aged seven years, he developed mumps meningoencephalitis, and had a cardiorespiratory arrest whilst unwell with this. He was then well until he suffered an acute intracerebral haemorrhage (involving the left caudate nucleus) aged 44 years, from which he made a good recovery, with only mild residual right-sided weakness. There was no family history of brain haemorrhage or cognitive impairment.

On examination at the time of admission, the patient had bilateral gaze-evoked nystagmus (longstanding), limb ataxia and stimulus-induced myoclonus in both upper limbs. There was increased tone in the left leg, in addition to residual right-sided weakness from his previous ICH; both plantar responses were extensor. He demonstrated significant global cognitive

difficulties with disorientation to place and person, garbled speech and disruptive visual and auditory hallucinations.

The presence of historical surgical clips precluded MRI; CT head imaging demonstrated extensive calcification, particularly in the basal ganglia (likely related to previous radiotherapy), and progressive atrophy. EEG demonstrated diffuse slow activity supportive of generalised cerebral dysfunction, but no periodic or epileptiform activity. CSF analyses demonstrated a significantly raised protein (5.89 g/l), reduced Aβ 42 (187 pg/ml; normal range 627 to 1322 pg/ml), and elevated total tau (4575 pg/ml; normal range 146 to 595 pg/ml). CSF 14-3-3 was negative; S100b was slightly elevated (762 pg/ml; normal <740 pg/ml). In order to exclude a potentially treatable diagnosis (such as cerebral vasculitis), a right frontal brain biopsy was performed. This demonstrated superficial cortical and leptomeningeal vascular Aβ deposition, as well as parenchymal Aβ plaques and tau pathology (including neuropil threads, occasional tangles and neuritic plaques)[3]. Amyloid-PET confirmed extensive Aβ deposition throughout the cortex and cerebellum. NGS did not detect mutations in genes associated with dementia (see note, Supplementary Table 1, for details of genes tested); further testing did not identify duplication of the *APP* gene. ApoE genotype was ε3/ε3.

The patient continued to deteriorate after discharge and died 4 months later (14 months after the onset of his cognitive symptoms).

Published case reports to date

Thirteen appropriate records were identified following our detailed search, which included details for 23 patients, one of whom was featured in two reports[4 5] and therefore counted only once; two cases were excluded as they were identified post-mortem and no clinical details were available[6]. Details of these cases, all but one of whom were diagnosed during life, are provided in full in Supplementary Table 2.

Details of the clinical features and key investigation findings are summarised in Table 1, with further individual details provided in Supplementary Tables 1 and 2. Table 2 provides a comparison of the clinical features of these iatrogenic cases with sporadic CAA.

TABLE 1
Summary of cases where the diagnosis of iatrogenic CAA was made during life.
Please see Supplementary Table 1 for individual details for the cases described in this report, and Supplementary Table 2 for further details of published cases to date.

			Previously reported cases (n=20)	Cases in this report (n=3)	All (n=23)
Age at first presentation, mean (SD), years			36.9 (8.3)	43.0 (3.6)	37.7 (8.1)
Sex, male, n (%)			15 (75.0)	2 (66.7)	17 (73.9)
Age at exposure, mean (range), years			3.3 (0.1 to 20.0)	4.0 (3.0 to 5.0)	3.3 (0.1 to 20.0)
Latency, mean (range), years			33.5 (25.0 to 46.0)	39.0 (36.0 to 42.0)	34.3 (25.0 to 46.0)
Exposure, n (%)	**Dura mater**		8 (40.0)	2 (66.7)	10 (43.5)
	Cadaveric dura mater		7 (35.0)	2 (66.7)	9 (39.1)
	Neurosurgery		17 (85.0)	1 (33.3)	18 (78.3)
ApoE genotype†, n (%)	**ε3**		18 (100.0)	3 (100.0)	21 (100.0)
	ε3/ε3		12 (66.7)	2 (66.7)	14 (66.7)
Presenting symptom, n (%)	**ICH (including cSAH)**		17 (85.0)	2 (66.7)	19 (82.6)
	Seizures		4 (20.0)	0 (0.0)	4 (17.4)
Associated symptoms, n (%)	**ICH**		17 (85.0)	3 (100.0)	20 (87.0)
	Recurrent ICH		14 (70.0)	1 (33.3)	15 (65.2)
	Cognitive impairment		6 (30.0)	3 (100.0)	9 (39.1)
	Seizures		6 (30.0)	0 (0.0)	6 (26.1)
Investigations					
MRI features of CAA	**cSS**	**Test performed, n**	10 (50.0)	2 (66.7)	12 (52.2)
		Present, n (%)	8 (80.0)	1 (50.0)	9 (75.0)
	CMB	**Test performed, n**	16 (80.0)	2 (66.7)	18 (78.3)
		Present, n (%)	16 (100.0)	2 (100.0)	18 (100.0)
Amyloid PET	**Test performed, n**		9 (45.0)	1 (33.3)	10 (43.4)
	Positive, n (%)		9 (100.0)	1 (100.0)	10 (100.0)
CSF findings	**Aβ-40**	**Test performed, n**	1 (100.0)	0 (0.0)	1 (4.3)
		Reduced, n (%)	1 (100.0)	0 (0.0)	1 (100.0)
	Aβ-42	**Test performed, n**	7 (35.0)	1 (33.3)	8 (34.8)

		Reduced, n (%)	7 (100.0)	1 (100.0)	8 (100.0)
	Total tau	**Test performed, n**	5 (25.0)	1 (33.3)	6 (26.1)
		High n (%)	1 (20.0)	1 (100.0)	2 (33.3)
	p-tau	**Test performed, n**	4 (20.0)	0 (0.0)	4 (17.3)
		High, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Brain biopsy	**Test performed, n**		12 (60.0)	3 (100.0)	15 (65.2)
	CAA observed, n (%)		12 (100.0)	3 (100.0)	15 (100.0)

Notes:

† ApoE genotype reported for 18 of 20 previously published cases

Abbreviations:

CMB, cerebral microbleed (lobar); cSAH, convexity SAH; cSS, cortical superficial siderosis; ICH, intracerebral haemorrhage; p-tau, phospho-tau; SD, standard deviation.

TABLE 2
Descriptive comparison of iatrogenic cases of CAA reported to date, compared with typical features of sporadic CAA

		Iatrogenic Cases (n=23)	**Sporadic CAA**	**References**
Age at first presentation		Mean 37.7 years	Associated with increasing age; rare in those under 60 years; current diagnostic criteria state age > 55 years	7-9
Sex		73.9% cases male	Pathologically more common in females; females more likely to have lobar ICH	7 10
ApoE genotype		ε3 present in all cases; homozygous in 66.7%	Usually associated with ε2 and ε4 genotypes	8 11
Associated symptoms	**ICH**	87.0% cases	Well recognised	12
	Recurrent ICH	65.2% cases	Well recognised; annual recurrence risk 7.4% (compared with 1.1% for non-CAA ICH)	12 13
	Cognitive impairment	39.1% cases	Well recognised	12
	TFNE	1 case	Well recognised	12 14
	Seizures	26.1% cases	Can occur but frequency unknown; recognised feature of CAA-related inflammation	12

Abbreviations:
ApoE, apolipoprotein E; CAA, cerebral amyloid angiopathy; ICH, intracerebral haemorrhage; TFNE, transient focal neurological episodes ("amyloid spells").

DISCUSSION

The experimental confirmation of human transmission of Aβ pathology resulting in CAA both introduced and established the concept of iatrogenic CAA[2]. In this report, we describe the clinical features of three patients with iatrogenic CAA (the pathological features having been reported by us previously[3]), two of whom underwent procedures using cadaveric dura, which further expands the clinical spectrum of this recently recognised condition. In common with previously reported cases, our patients had early onset of symptoms, and all had previous medical procedures where Aβ transmission could have taken place, with a latency of three or four decades and exposure occurring in the early 1980s. Two of our cases are likely to have been exposed to Aβ during embolisation procedures using cadaveric dura mater, a method of transmission previously reported by us[15] and others[16]. One of our patients (Case 2) presented with transient focal neurological episodes (TFNE, sometimes termed "amyloid spells"[14]), a well-recognised clinical feature of sporadic CAA but as yet undescribed in iatrogenic cases. We also describe a rapidly progressive cognitive presentation (again previously not described in iatrogenic CAA) with associated features of ataxia and myoclonus that are more commonly observed in prion diseases. Together, these cases illustrate an expanding spectrum of possible presenting features and natural histories that can be associated with iatrogenic CAA.

The concept of proteinaceous infectious particles ("prions")[17] is well-established, and best studied in relation to diseases involving the prion protein, particularly Creutzfeldt-Jakob disease (CJD) which can be sporadic, inherited or acquired (including iatrogenic exposures)[18]. Following transmission, prions comprised of fibrillar assemblies of misfolded cellular prion protein, are able to act as a template, thereby converting host prion protein into disease-associated forms[18]. These and other properties thought to be peculiar to the prion protein are increasingly recognised as having have relevance to other aggregating proteins seen in neurodegenerative diseases, including amyloid-beta[18]. Evidence for amyloid-beta transmission in animal models has existed for many years[19-22]; the existence of amyloid-beta

proteopathic seeds within cadaveric material (as has been shown in historical samples of cadaveric human growth hormone[2] and autopsy dura samples[23]), or on neurosurgical instruments (acquired after initial use on patients with amyloid-beta disease with inadequate decontamination afterwards) could explain transmission of amyloid-beta pathology between people. Acquired forms of diseases caused by the prion protein (including iatrogenic CJD, variant CJD and Kuru) are characterised by lengthy incubation periods (up to several decades); iatrogenic amyloid-beta transmission appears to have a similarly long latency between exposure and clinical presentation. Experimental work suggests that this is because prions propagate in a new host in two distinct phases[18 24]: an initial clinically-silent phase, characterised by an exponential increase in infectivity until saturation (i.e. when the concentration of prions reaches a maximal level, and a second plateau phase where prion levels remain relatively constant during which time toxicity (neurodegeneration) and subsequent clinical deterioration occur. Future work on the kinetics of amyloid-beta propagation is needed to explore whether similar mechanisms underlie the long latency observed in iatrogenic CAA.

There are important similarities and differences between iatrogenic and sporadic CAA (Table 2), which are of clinical and potential pathophysiological relevance. Although the cases reported to date are younger than sporadic cases, this likely reflects the early age at which they were exposed to Aβ seeds; people exposed at older ages who then develop iatrogenic CAA might not be as obviously identifiable, given that they fall within the age range for sporadic disease. Although the number of iatrogenic cases reported to date is relatively small, these show a male predominance (sporadic CAA is relatively balanced across sex, although pathologically more common in females, who also have an increased rate of lobar ICH) and there is no particular association with the ApoE ε2 and ε4 alleles (an association frequently described in sporadic CAA). Whilst ICH, and in particular recurrent ICH, seems to be a feature of both iatrogenic and sporadic cases, seizures and rapidly progressive cognitive impairment can also be presenting features in iatrogenic cases. The association between sporadic CAA

and cognitive impairment is well recognised[12], but it is less common for progressive cognitive impairment to be the presenting symptom; by contrast, rapidly progressive cognitive symptoms are typically observed in the inflammatory form of CAA[25].

Of note, the patients described in this report also showed evidence of pathologies associated with Alzheimer's disease (parenchymal Aβ, tau neurofibrillary tangle pathology in the neocortex), which are highly unusual in people under the age of 50 (particularly in the absence of relevant gene mutations) and might contribute to the cognitive features observed. Seizures are a well-recognised post-stroke complication, particularly in young patients with intracerebral haemorrhage[26 27]. It is not clear whether the relatively high prevalence of seizures in iatrogenic CAA cases is simply a consequence of younger age at presentation, or reflects an independent disease mechanism; certain imaging features observed in iatrogenic cases that are atypical for sporadic CAA might be particularly epileptogenic (for example, cortical swelling). Four reported cases had features atypical for CAA, namely non-lobar (thalamic) ICH[4 5 28] and lacunar infarction[5]; these are usually attributed to deep perforator arteriopathy (also termed hypertensive arteriopathy), another common age-related cerebral small vessel disease. In neither case was there a significant history of hypertension or treatment with radiotherapy (another cause for cerebral small vessel damage) noted. One of our cases similarly presented with a non-lobar ICH, but the clinical impression was that this was incidental to the diagnosis of CAA, and instead secondary to radiotherapy-associated small vessel disease. Although we have presented all available information, given the relatively small number of cases reported to date and the risk of ascertainment bias (with early onset cases with unusual clinical features more likely to be referred to specialist centres, where the diagnosis can be made), it is difficult to draw firm conclusions about these presenting features, highlighting the importance for identifying further cases.

The current case series, together with previously published cases, demonstrate the variability in investigative approaches, particularly in cases where alternative diagnoses were being

considered. We suggest that standardisation of this approach should be attempted where possible, and we provide proposed diagnostic criteria based on all available case reports in Table 3. From the cases reported so far, iatrogenic CAA seems to share MRI features with sporadic CAA, namely the presence of haemorrhagic structural imaging markers including cerebral microbleeds and cortical superficial siderosis[9]. Brain Aβ deposition can additionally be confirmed using amyloid-PET, although this is not specific for Aβ and therefore should not be used in isolation[29], and via CSF analyses; the presence of reduced CSF Aβ-40 and Aβ-42, with normal total tau and phospho-tau levels is particularly suggestive of CAA[30 31]. Genetic testing to exclude mutations or duplications associated with early onset, familial forms of Aβ disease is essential, as these conditions are the main alternative diagnosis for iatrogenic cases, and wider testing to exclude rare genetic causes of non-Aβ CAA should also be considered in certain cases, guided by clinical features. We therefore suggest use of these modalities (MRI, amyloid-PET, CSF analysis, genetic testing) in the first instance; brain biopsy should be considered in cases where the presentation is atypical, or a significant alternative diagnosis remains highly probable and has implications for subsequent management, for example cerebral vasculitis or iatrogenic prion disease (where RT-QuIC analyses are less reliable diagnostically[32 33]). Some tests (for example, amyloid-PET, comprehensive genetic testing) might not be available at all centres, and in these cases involvement of clinicians and institutions with clinical and/or research expertise in CAA might be advisable.

TABLE 3
Proposed diagnostic criteria for probable iatrogenic CAA

In order for a diagnosis of probable iatrogenic CAA to be made during life, criteria 2, 3, 4 and 5 must be met as a minimum. Features in the history which are strongly suggestive of the diagnosis are highlighted.

A diagnosis of possible iatrogenic CAA can be considered if criteria 1, 2 and 3 are met.

1. Age of onset
• Symptom onset before age of 55 years (i.e. below the age threshold for "probable" or "possible" CAA within the modified Boston criteria[9]); **strongly suggestive (although note ascertainment bias)** • *Note: diagnosis cannot be excluded based on age alone, and should be considered in people aged 55 years or above, should they meet the other criteria (detailed below)*
2. History of potential exposure; *one or more of the following*:
• Procedure or treatment using cadaveric human CNS tissues (i.e. brain, meninges, pituitary-derived hormones); **strongly suggestive** • Relevant neurosurgical procedure (i.e. those involving the brain, spinal cord, posterior eye) • *Note: diagnosis can be considered if history of alternative potential exposure and all other criteria are met*
3. Clinical and radiological features consistent with a diagnosis of CAA:
Clinical: • Evidence of at least one of the following features, either at presentation or during disease course: o Intracerebral haemorrhage or convexity subarachnoid haemorrhage (single or multiple) o Transient focal neurological episodes ("amyloid spells") o Focal seizures (with or without secondary generalisation) o Cognitive impairment not attributable to another cause (including acute stroke) Radiological; at least one of the following: • CT: o Lobar intracerebral haemorrhage o Convexity subarachnoid haemorrhage • MRI (blood sensitive sequences; T2*-GRE, SWI): o Cerebral microbleeds with predominantly lobar distribution, distant from sites of parenchymal intracerebral haemorrhage o Cortical superficial siderosis (focal or disseminated) on MR blood sensitive sequences
4. Evidence of amyloid-beta (Aβ) accumulation in the CNS:
• Positive amyloid-PET scan (note this is not specific for vascular amyloid-beta deposition) • Supportive CSF features (reductions of Aβ-42, Aβ-40)

- Brain biopsy demonstrating vascular Aβ deposition, in the absence of significant inflammation

- *Notes:*
  - *A positive amyloid-PET scan in isolation might not necessarily specific for Aβ accumulation, depending on the tracer used[29]; correlation with either CSF Aβ measures, brain biopsy findings and/or genetic testing for non-Aβ CAAs (details below) is advised*
  - *Presence of significant inflammation might support an alternative diagnosis of CAA-related inflammation or amyloid-beta related angiitis (ABRA)[34]*

5. Exclusion of genetic causes of amyloid-beta (Aβ) CNS disease; *this should include*:

- Duplications of APP (including Trisomy 21, where relevant)
- Mutations of APP, PSEN1, PSEN2

- In cases where CNS Aβ deposition has not been confirmed by other means (CSF Aβ measures, brain biopsy), next generation sequencing for mutations resulting in non-Aβ CAA (*CST3*, *TTR*, *GSN*, *PRNP*, *ITM2B)* should be considered

Questions remain about potential exposures and strategies to prevent further cases. The use of cadaveric human materials is restricted in most countries given the risk of iatrogenic CJD; it is difficult to know exactly how many people have been exposed to due to variations in central record keeping. Prions can be transmitted via contaminated neurosurgical instruments and blood transfusions, and iatrogenic cases of CJD have been reported in association with both of these exposures[35]. Our review identified twelve cases of iatrogenic CAA following neurosurgical procedures without exposure to cadaveric material, although proper ascertainment of this via historical records can be challenging. There is evidence from transgenic mice that amyloid-beta can be transmitted via steel wires, and that transmission can be prevented by plasma sterilisation, but not boiling[21]. There are no reported cases of iatrogenic CAA associated with blood transfusions in humans and epidemiological data to date do not support this[35], but there is experimental data suggesting that amyloid-beta transmission can occur via this route[36]. Large epidemiological studies are needed to fully evaluate the risk of amyloid-beta transmission via contaminated instruments; this will inform future decision making regarding appropriate instrument sterilisation that prevent amyloid-beta transmission, methods for which also require further investigation.

Alternative explanations for the presence of early-onset CAA in these and similar patients have been proposed, most notably the potential impact of traumatic brain injury (TBI)[37-39]. Amyloid-beta rapidly accumulates in the acute phase following TBI[40 41], perhaps due to disruption of the blood brain barrier[42 43], and then usually clears over a period of days[44 45]. Disentangling the role of TBI is challenging, as the injuries sustained in reported cases might have warranted neurosurgical intervention (either with or without cadaveric material); certainly the interval between brain injury and clinical presentation with symptomatic CAA would be in keeping with the latency expected for iatrogenic transmission of amyloid-beta. These reports do not mention whether neurosurgical procedures were needed, and it is not clear whether this is because historical information regarding this is lacking, or whether they truly did not take place. Moreover, not all patients with evidence of early-onset CAA have a preceding history of TBI, including those exposed to cadaveric dura mater via embolization procedures (included two of the cases in this report, in addition to two others[15 16]) or cardiac procedures[46], and those who received cadaveric human growth hormone as children[6]; these cadaveric materials are all well-recognised as vehicles for prion protein transmission in the context of CJD[47-49]. In view of these points, and the robust experimental evidence for amyloid-beta transmission, it is our opinion that mechanism for early-onset CAA in TBI is likely iatrogenic protein transmission, as in our cases, and that further retrospective interrogation of historical medical records may help to further clarify.

Clinical details for the three cases reported here further expand the spectrum of presenting features for iatrogenic CAA. Cases have now been recognised worldwide, and it is likely that as more are described and published, our understanding of this unusual form of CAA will continue to expand. Confirming the means by which Aβ transmission can occur will have important public health implications for preventing future cases. We advise clinicians to remain vigilant for an iatrogenic cause when seeing patients with an early onset form of CAA, by

specifically enquiring about previous medical procedures where Aβ transmission could have taken place.

FUNDING

GB holds a Clinical Lectureship funded by Alzheimer's Research UK (ARUK-CRF2020A-003), the Stroke Association (SA L-MP 20\100002) and the NIHR (no award/grant number). ZJ, AKT, SFF and SB are supported by the UK Department of Health's NIHR Biomedical Research Centre's funding scheme to UCLH (no award/grant number). SM and JC are NIHR Senior Investigators (NF-SI-0617-10175 and NF-SI-0611-10073 respectively). The MRC Prion Unit at UCL is core funded by the UK Medical Research Council (no award/grant number).

DATA AVAILABILITY

Available anonymised data are provided in the manuscript and supplementary material.

RESEARCH ETHICS APPROVAL

Written consent has been obtained for those patients living at the time of manuscript preparation.

COMPETING INTERESTS

The authors report no relevant competing interests.

CONTRIBUTORSHIP

GB designed and conceptualized study, collected the clinical data, performed the literature searches, and drafted the manuscript. KS collected the clinical data and revised the manuscript for intellectual content. MEA prepared Figure 2, and revised the manuscript for intellectual content. ZJ and SB contributed to the neuropathological data, and revised the

manuscript for intellectual content. APJ, JG, AKT, SFF, RS, PR and JMS all contributed to the clinical care of the patients described, and revised the manuscript for intellectual content. HH, SM and JC contributed the genetic analyses, and revised the manuscript for intellectual content. DJW contributed to the clinical care of the patients and the design and conceptualization of the study, and revised the manuscript for intellectual content.

ACKNOWLEDGEMENTS

We would like to thank Kate Brunskill, Deputy Librarian at the Queen Square Library (UCL Queen Square Institute of Neurology & The National Hospital for Neurology & Neurosurgery) for her assistance in refining the search strategies required for this report. We would also like to acknowledge the contribution of colleagues, at our institutions and elsewhere, in caring for the patients described.

References

1. Jaunmuktane Z, Mead S, Ellis M, et al. Evidence for human transmission of amyloid-beta pathology and cerebral amyloid angiopathy. *Nature* 2015;525(7568):247-50. doi: 10.1038/nature15369 [published Online First: 2015/09/12]

2. Purro SA, Farrow MA, Linehan J, et al. Transmission of amyloid-beta protein pathology from cadaveric pituitary growth hormone. *Nature* 2018;564(7736):415-19. doi: 10.1038/s41586-018-0790-y [published Online First: 2018/12/14]

3. Jaunmuktane Z, Banerjee G, Paine S, et al. Alzheimer's disease neuropathological change three decades after iatrogenic amyloid-beta transmission. *Acta neuropathologica* 2021;142(1):211-15. doi: 10.1007/s00401-021-02326-y [published Online First: 2021/05/29]

4. Jaunmuktane Z, Quaegebeur A, Taipa R, et al. Evidence of amyloid-beta cerebral amyloid angiopathy transmission through neurosurgery. *Acta neuropathologica* 2018;135(5):671-79. doi: 10.1007/s00401-018-1822-2 [published Online First: 2018/02/17]

5. Michiels L, Van Weehaeghe D, Vandenberghe R, et al. The Role of Amyloid PET in Diagnosing Possible Transmissible Cerebral Amyloid Angiopathy in Young Adults with a History of Neurosurgery: A Case Series. *Cerebrovascular diseases (Basel, Switzerland)* 2021;50(3):356-60. doi: 10.1159/000514139 [published Online First: 2021/03/22]

6. Ritchie DL, Adlard P, Peden AH, et al. Amyloid-beta accumulation in the CNS in human growth hormone recipients in the UK. *Acta neuropathologica* 2017;134(2):221-40. doi: 10.1007/s00401-017-1703-0 [published Online First: 2017/03/30]

7. Arvanitakis Z, Leurgans SE, Wang Z, et al. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. *Annals of neurology* 2011;69(2):320-7. doi: 10.1002/ana.22112 [published Online First: 2011/03/10]

8. Greenberg SM. Cerebral Amyloid Angiopathy. In: Kasner SE, ed. UpToDate. Waltham, MA2020.

9. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74(17):1346-50. doi: 10.1212/WNL.0b013e3181dad605 [published Online First: 2010/04/28]

10. Roquer J, Rodriguez-Campello A, Jimenez-Conde J, et al. Sex-related differences in primary intracerebral hemorrhage. *Neurology* 2016;87(3):257-62. doi: 10.1212/WNL.0000000000002792 [published Online First: 2016/06/10]

11. Rannikmae K, Kalaria RN, Greenberg SM, et al. APOE associations with severe CAA-associated vasculopathic changes: collaborative meta-analysis. *Journal of neurology, neurosurgery, and psychiatry* 2014;85(3):300-5. doi: 10.1136/jnnp-2013-306485 [published Online First: 2013/10/29]

12. Banerjee G, Carare R, Cordonnier C, et al. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. *Journal of neurology, neurosurgery, and psychiatry* 2017;88(11):982-94. doi: 10.1136/jnnp-2016-314697 [published Online First: 2017/08/28]

13. Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. *Neurology* 2017;89(8):820-29. doi: 10.1212/WNL.0000000000004259 [published Online First: 2017/07/28]

14. Smith EE, Charidimou A, Ayata C, et al. Cerebral Amyloid Angiopathy-Related Transient Focal Neurologic Episodes. *Neurology* 2021;97(5):231-38. doi: 10.1212/WNL.0000000000012234 [published Online First: 2021/05/22]

15. Banerjee G, Adams ME, Jaunmuktane Z, et al. Early onset cerebral amyloid angiopathy following childhood exposure to cadaveric dura. *Annals of neurology* 2019;85(2):284-90. doi: 10.1002/ana.25407 [published Online First: 2019/01/01]

16. Caroppo P, Marucci G, Maccagnano E, et al. Cerebral amyloid angiopathy in a 51-year-old patient with embolization by dura mater extract and surgery for nasopharyngeal angiofibroma at age 17. *Amyloid* 2021;28(2):142-43. doi: 10.1080/13506129.2020.1854715 [published Online First: 2020/12/05]

17. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. *Science (New York, NY)* 1982;216(4542):136-44. doi: 10.1126/science.6801762 [published Online First: 1982/04/09]

18. Collinge J. Mammalian prions and their wider relevance in neurodegenerative diseases. *Nature* 2016;539(7628):217-26. doi: 10.1038/nature20415 [published Online First: 2016/11/11]

19. Baker HF, Ridley RM, Duchen LW, et al. Evidence for the experimental transmission of cerebral beta-amyloidosis to primates. *Int J Exp Pathol* 1993;74(5):441-54. [published Online First: 1993/10/01]

20. Baker HF, Ridley RM, Duchen LW, et al. Experimental induction of beta-amyloid plaques and cerebral angiopathy in primates. *Ann N Y Acad Sci* 1993;695:228-31. doi: 10.1111/j.1749-6632.1993.tb23057.x [published Online First: 1993/09/24]

21. Eisele YS, Bolmont T, Heikenwalder M, et al. Induction of cerebral β-amyloidosis: Intracerebral versus systemic Aβ inoculation. *Proceedings of the National Academy of Sciences* 2009;106(31):12926-31. doi: 10.1073/pnas.0903200106

22. Eisele YS, Obermuller U, Heilbronner G, et al. Peripherally applied Abeta-containing inoculates induce cerebral beta-amyloidosis. *Science (New York, NY)* 2010;330(6006):980-2. doi: 10.1126/science.1194516 [published Online First: 2010/10/23]

23. Kovacs GG, Lutz MI, Ricken G, et al. Dura mater is a potential source of Abeta seeds. *Acta neuropathologica* 2016;131(6):911-23. doi: 10.1007/s00401-016-1565-x [published Online First: 2016/03/27]

24. Sandberg MK, Al-Doujaily H, Sharps B, et al. Prion propagation and toxicity in vivo occur in two distinct mechanistic phases. *Nature* 2011;470(7335):540-2. doi: 10.1038/nature09768 [published Online First: 2011/02/26]

25. Corovic A, Kelly S, Markus HS. Cerebral amyloid angiopathy associated with inflammation: A systematic review of clinical and imaging features and outcome. *International journal of stroke : official journal of the International Stroke Society* 2018;13(3):257-67. doi: 10.1177/1747493017741569 [published Online First: 2017/11/15]

26. De Herdt V, Dumont F, Henon H, et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. *Neurology* 2011;77(20):1794-800. doi: 10.1212/WNL.0b013e31823648a6 [published Online First: 2011/10/07]

27. Haapaniemi E, Strbian D, Rossi C, et al. The CAVE score for predicting late seizures after intracerebral hemorrhage. *Stroke* 2014;45(7):1971-6. doi: 10.1161/STROKEAHA.114.004686 [published Online First: 2014/05/31]

28. Herve D, Porche M, Cabrejo L, et al. Fatal Abeta cerebral amyloid angiopathy 4 decades after a dural graft at the age of 2 years. *Acta neuropathologica* 2018;135(5):801-03. doi: 10.1007/s00401-018-1828-9 [published Online First: 2018/03/07]

29. Hellstrom-Lindahl E, Westermark P, Antoni G, et al. In vitro binding of [(3)H]PIB to human amyloid deposits of different types. *Amyloid* 2014;21(1):21-7. doi: 10.3109/13506129.2013.860895 [published Online First: 2013/11/30]

30. Banerjee G, Ambler G, Keshavan A, et al. Cerebrospinal Fluid Biomarkers in Cerebral Amyloid Angiopathy. *Journal of Alzheimer's disease : JAD* 2020;74(4):1189-201. doi: 10.3233/JAD-191254 [published Online First: 2020/03/17]

31. Charidimou A, Friedrich JO, Greenberg SM, et al. Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy: A meta-analysis. *Neurology* 2018;90(9):e754-e62. doi: 10.1212/WNL.0000000000005030 [published Online First: 2018/02/02]

32. Green AJE. RT-QuIC: a new test for sporadic CJD. *Practical neurology* 2019;19(1):49-55. doi: 10.1136/practneurol-2018-001935 [published Online First: 2018/10/05]

33. Llorens F, Villar-Pique A, Hermann P, et al. Diagnostic Accuracy of Prion Disease Biomarkers in Iatrogenic Creutzfeldt-Jakob Disease. *Biomolecules* 2020;10(2) doi: 10.3390/biom10020290 [published Online First: 2020/02/16]

34. Auriel E, Charidimou A, Gurol ME, et al. Validation of Clinicoradiological Criteria for the Diagnosis of Cerebral Amyloid Angiopathy-Related Inflammation. *JAMA neurology* 2016;73(2):197-202. doi: 10.1001/jamaneurol.2015.4078 [published Online First: 2016/01/01]

35. Lauwers E, Lalli G, Brandner S, et al. Potential human transmission of amyloid beta pathology: surveillance and risks. *The Lancet Neurology* 2020;19(10):872-78. doi: 10.1016/S1474-4422(20)30238-6 [published Online First: 2020/09/20]

36. Bu XL, Xiang Y, Jin WS, et al. Blood-derived amyloid-β protein induces Alzheimer's disease pathologies. *Mol Psychiatry* 2018;23(9):1948-56. doi: 10.1038/mp.2017.204 [published Online First: 2017/11/01]

37. Purrucker JC, Hund E, Ringleb PA, et al. Cerebral amyloid angiopathy--an underdiagnosed entity in younger adults with lobar intracerebral hemorrhage? *Amyloid* 2013;20(1):45-7. doi: 10.3109/13506129.2012.746937 [published Online First: 2012/12/13]

38. Nakayama Y, Mineharu Y, Arawaka Y, et al. Cerebral amyloid angiopathy in a young man with a history of traumatic brain injury: a case report and review of the literature. *Acta Neurochir (Wien)* 2017;159(1):15-18. doi: 10.1007/s00701-016-3004-0 [published Online First: 2016/11/05]

39. Oblak JP, Jurecic A, Writzl K, et al. Preceding Head Trauma in Four Cases of Sporadic Cerebral Amyloid Angiopathy - Case Report Series. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2021;31(2):106260. doi: 10.1016/j.jstrokecerebrovasdis.2021.106260 [published Online First: 2021/12/22]

40. Roberts GW, Gentleman SM, Lynch A, et al. Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. *Journal of neurology, neurosurgery, and psychiatry* 1994;57(4):419-25. doi: 10.1136/jnnp.57.4.419 [published Online First: 1994/04/01]

41. Roberts GW, Gentleman SM, Lynch A, et al. beta A4 amyloid protein deposition in brain after head trauma. *Lancet (London, England)* 1991;338(8780):1422-3. doi: 10.1016/0140-6736(91)92724-g [published Online First: 1991/12/07]

42. Shlosberg D, Benifla M, Kaufer D, et al. Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nature reviews Neurology* 2010;6(7):393-403. doi: 10.1038/nrneurol.2010.74 [published Online First: 2010/06/17]

43. Abrahamson EE, Ikonomovic MD. Brain injury-induced dysfunction of the blood brain barrier as a risk for dementia. *Exp Neurol* 2020;328:113257. doi: 10.1016/j.expneurol.2020.113257 [published Online First: 2020/02/25]

44. Chen XH, Johnson VE, Uryu K, et al. A lack of amyloid beta plaques despite persistent accumulation of amyloid beta in axons of long-term survivors of traumatic brain injury. *Brain Pathol* 2009;19(2):214-23. doi: 10.1111/j.1750-3639.2008.00176.x [published Online First: 2008/05/22]

45. Hong YT, Veenith T, Dewar D, et al. Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. *JAMA neurology* 2014;71(1):23-31. doi: 10.1001/jamaneurol.2013.4847 [published Online First: 2013/11/13]

46. Raposo N, Planton M, Siegfried A, et al. Amyloid-beta transmission through cardiac surgery using cadaveric dura mater patch. *Journal of neurology, neurosurgery, and psychiatry* 2020;91(4):440-41. doi: 10.1136/jnnp-2019-321927 [published Online First: 2020/01/22]

47. Antoine JC, Michel D, Bertholon P, et al. Creutzfeldt-Jakob disease after extracranial dura mater embolization for a nasopharyngeal angiofibroma. *Neurology* 1997;48(5):1451-3. doi: 10.1212/wnl.48.5.1451 [published Online First: 1997/05/01]

48. Defebvre L, Destee A, Caron J, et al. Creutzfeldt-Jakob disease after an embolization of intercostal arteries with cadaveric dura mater suggesting a systemic transmission of the prion agent. *Neurology* 1997;48(5):1470-1. doi: 10.1212/wnl.48.5.1470 [published Online First: 1997/05/01]

49. Watson N, Brandel JP, Green A, et al. The importance of ongoing international surveillance for Creutzfeldt-Jakob disease. *Nature reviews Neurology* 2021;17(6):362-79. doi: 10.1038/s41582-021-00488-7 [published Online First: 2021/05/12]

Figure 1: PRISMA flowchart for case selection.

Figure 2: Brain imaging from Cases 1 and 2

Case 1 (a,b,c,d). CT (a) at first presentation demonstrates an acute right parietal lobar haematoma with finger-like projections into the parenchyma. T2-weighted (b) and SWI images (c, d) 10 months after the initial haemorrhage demonstrate a mature, haemosiderin-lined gliotic cavity at the site of the haematoma with numerous microbleeds in the adjacent parenchyma, visible as punctate foci of low signal.

Case 2 (e,f,g,h). FLAIR (e) at first presentation shows evidence of recent subarachnoid haemorrhage, visible as high signal within the right parietal sulci. SWI (f) at the time of the first MRI also shows multifocal superficial siderosis, visualized as low signal lining multiple gyri, and a small number of peripheral microbleeds. SWI (g) 14 months after the first scan shows an increase in the extent of the superficial siderosis. T2-weighted image (h) 2 weeks later demonstrates a new right frontal lobar haematoma.