Review

Iatrogenic cerebral amyloid angiopathy: an emerging clinical phenomenon

Gargi Banerjee,1,2 Kiran Samra,3 Matthew E Adams,4 Zane Jaunmuktane,4,5 Adrian Robert Parry-Jones,6,7 Joan Grieve,8 Ahmed K Toma,8 Simon F Farmer,9 Richard Sylvester,9 Henry Houlden,10 Peter Rudge,1 Simon Mead,1,10 Sebastian Brandner,1,2,4 Jonathan M Schott,1,2 John Collinge,1 David J Werring10

ABSTRACT

In the last 6 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, but also seizures and cognitive impairment. Although assumed to be rare, it is important that clinicians remain vigilant for potential cases, particularly as assumed to be rare, it is important that clinicians remain vigilant for potential cases, particularly as cases with coexisting iatrogenic Creutzfeldt-Jakob disease (CJD) were excluded, as coexistence of this diagnosis would likely mask a clinical presentation of iatrogenic CAA.

We provide clinical details for three patients with pathological evidence of iatrogenic CAA and present a summary of the published cases to date. Our aims are: (1) To review 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.

INTRODUCTION

In the 6 years following the first pathological description of presumed amyloid-beta (Aβ) transmission in humans1 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. 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, reviewing similar cases and differences between iatrogenic and sporadic CAA; and (2) To discuss potential approaches for investigation and diagnosis, including suggested diagnostic criteria for iatrogenic CAA.

MATERIALS AND METHODS

The following search strategies were used:

PubMed (Medline)
(‘cerebral amyloid angiopathy’(MeSH Terms) OR ‘vascular amyloidosis’(tw) OR (cerebral(tw) AND ‘amyloid angiopathy’(tw))) AND (‘cadaver’(MeSH Terms) OR ‘cadaver’(tw) OR ‘iatrogenic disease’(MeSH Terms) OR iatrogen*(tw) OR ‘prion diseases’(MeSH Terms) OR ‘prion’(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 angiopathy.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 exp neurosurgery*.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 coexisting iatrogenic Creutzfeldt-Jakob disease (CJD) were excluded, as coexistence 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
Cerebrovascular disease

A man in his late 30s presented with headache, left-sided retroorbital pain and a left homonymous hemianopia, and shortly afterwards developed left-sided weakness and became obtunded. Immediate CT imaging identified an acute right parietal ICH (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 hemispheres) demonstrated further regions of superficial siderosis in both cerebral hemispheres (figure 2; panel G). Neuropsychometry at this stage demonstrated mild visuospatial underfunctioning 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 woman in her mid 40s presented with four stereotyped episodes of left-sided sensory symptoms (paraesthesia, ‘coldness’) which spread over 5 min from her shoulder into her hand. Two of them occurred within a few days, and a further two over the next 3 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 long-standing 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 8 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. MRI demonstrated further regions of superficial siderosis in both cerebral hemispheres (figure 2; panel G). Neuropsychometry at this stage demonstrated mild-to-moderate non-verbal underfunctioning 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, online supplemental 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 postauricular 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’ polyanvin 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 underfunctioning 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 REPORTS

Case 1

A man in his late 30s presented with headache, left-sided retroorbital pain and a left homonymous hemianopia, and shortly afterwards developed left-sided weakness and became obtunded. Immediate CT imaging identified an acute right parietal ICH (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 hemispheres) demonstrated further regions of superficial siderosis in both cerebral hemispheres (figure 2; panel G). Neuropsychometry at this stage demonstrated mild-to-moderate non-verbal underfunctioning 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, online supplemental table 1, for details of genes tested), further testing did not identify duplication of the APP gene.

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for case selection. CJD, Creutzfeldt-Jakob disease.

Precipitant reported (ie, a procedure involving the brain, spinal cord or posterior eye, or one using human cadaveric material) were excluded. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for record inclusion.

Premortem diagnosis was defined as diagnosis made during life, based on clinical presentation, brain imaging and/or brain biopsy. Postmortem diagnosis is used where the diagnosis was made after death.


Figure 1, for details of genes tested); further testing did not identify duplication of the APP gene.

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Table 1, for details of genes tested); further testing did not identify duplication of the APP gene.
in NOTCH3 (c.2183 G>A; 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 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 pretangles, occasional tangles, and occasional neuritic plaques containing both Aβ and tau). She was discharged after a 2-week admission, and made good improvements in her left hand function in the months following this. Seven months later, she presented again with sudden-onset dysphasia and reduced conscious level; CT revealed a new left frontal lobe ICH. Her hospital admission (lasting 6 months) was complicated by a traumatic left-sided subdural haemorrhage requiring a burr hole and surgical evacuation (approximately 2 months into her admission), a further ICH (left frontal, near the surgical site, day 1 postoperatively), and generalised seizures (starting 2 weeks postoperatively). Approximately 6 months following her discharge, she had a further ICH and died shortly thereafter.

**Case 3**

A man 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 postoperative whole brain and spine radiotherapy, and 2 years later required a ventriculoperitoneal 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 7 years, he had developed mumps meningoencephalitis, and had a cardiorespiratory arrest while unwell with this. He was then well until he suffered an acute ICH (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.
Cerebrovascular disease

On examination at the time of admission, the patient had bilateral gaze-evoked nystagmus (long-standing), 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 627–1322 pg/mL), and elevated total tau (4575 pg/mL; normal range 146–595 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). Amyloid-PET confirmed extensive Aβ deposition throughout the cortex and cerebellum. ApoE genotype was ε3/ε3. NGS did not detect mutations in genes associated with dementia (see note, online supplemental table 1, for details of genes tested); further testing did not identify duplication of the APP gene.

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 and therefore counted only once; two cases were excluded as they were identified postmortem and no clinical details were available. Details of these cases, all but one of whom were diagnosed during life, are provided in full in online supplemental table 2.

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

DISCUSSION

In this report, we describe the clinical features of three patients with iatrogenic CAA (the pathological features having been reported by us previously) 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. 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 and others.

One of our patients (Case 2) presented with transient focal neurological episodes (sometimes termed ‘amyloid spells’), 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 range of possible presenting features and natural histories that can be associated with iatrogenic CAA.

The concept of proteinaceous infectious particles (prions) is well established, and best studied in relation to diseases involving the prion protein, particularly CJD, which can be sporadic, inherited or acquired (including iatrogenic exposures).

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.

These and other properties thought to be peculiar to the prion protein are increasingly recognised as having relevance to other aggregating proteins seen in neurodegenerative diseases, including Aβ. Evidence for Aβ transmission in animal models has existed for many years; the existence of Aβ proteopathic seeds; including Aβ deposition in cerebrovascular material (as has been shown in historical samples of cadaveric human growth hormone and autopsy dura samples) or on neurosurgical instruments (acquired after initial use on patients with Aβ disease with inadequate decontamination afterwards) could explain transmission of Aβ 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 Aβ 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: an initial clinically silent phase, characterised by an exponential increase in infectivity until saturation (ie, 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 Aβ 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 generally balanced across sex, although pathologically more common in women, 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). While 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, 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.

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 years (particularly in the absence of relevant gene mutations).
### Table 1  Summary of clinical features and key investigation findings in reported cases of iatrogenic CAA

<table>
<thead>
<tr>
<th></th>
<th>Previously reported cases (n=20)</th>
<th>Cases in this report (n=3)</th>
<th>All (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first presentation, mean (SD), years</td>
<td>36.9 (8.3)</td>
<td>43.0 (3.6)</td>
<td>37.7 (8.1)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>15 (75.0)</td>
<td>2 (66.7)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Age at first exposure, mean (range), years</td>
<td>3.3 (0.1 to 20.0)</td>
<td>4.0 (3.0 to 5.0)</td>
<td>3.3 (0.1 to 20.0)</td>
</tr>
<tr>
<td>Latency, mean (range), years</td>
<td>33.5 (25.0 to 46.0)</td>
<td>39.0 (36.0 to 42.0)</td>
<td>34.3 (25.0 to 46.0)</td>
</tr>
<tr>
<td>Exposure, n (%)</td>
<td>Dura mater 8 (40.0)</td>
<td>2 (66.7)</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td></td>
<td>Cadaveric dura mater 7 (35.0)</td>
<td>2 (66.7)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td></td>
<td>Neurosurgery 17 (85.0)</td>
<td>1 (33.3)</td>
<td>18 (78.3)</td>
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<tr>
<td>ApoE genotype*, n (%)</td>
<td>ε3 18 (100.0)</td>
<td>3 (100.0)</td>
<td>21 (100.0)</td>
</tr>
<tr>
<td></td>
<td>ε3/ε3 12 (66.7)</td>
<td>2 (66.7)</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td>Presenting symptom, n (%)</td>
<td>ICH (including cSAH) 17 (85.0)</td>
<td>2 (66.7)</td>
<td>19 (82.6)</td>
</tr>
<tr>
<td></td>
<td>Seizures 4 (20.0)</td>
<td>0 (0.0)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Associated symptoms, n (%)</td>
<td>ICH 17 (85.0)</td>
<td>3 (100.0)</td>
<td>20 (87.0)</td>
</tr>
<tr>
<td></td>
<td>Recurrent ICH 14 (70.0)</td>
<td>1 (33.3)</td>
<td>15 (65.2)</td>
</tr>
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<td></td>
<td>Cognitive impairment 6 (30.0)</td>
<td>3 (100.0)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td></td>
<td>Seizures 6 (30.0)</td>
<td>0 (0.0)</td>
<td>6 (26.1)</td>
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<tr>
<td>Investigations</td>
<td>MRI features of CAA</td>
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<td></td>
<td>cSS Reported, n 10</td>
<td>2</td>
<td>12</td>
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<td></td>
<td>Present, n (%) 8 (80.0)</td>
<td>1 (50.0)</td>
<td>9 (75.0)</td>
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<td></td>
<td>CMB Reported, n 16</td>
<td>2</td>
<td>18</td>
</tr>
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<td></td>
<td>Present, n (%) 16 (100.0)</td>
<td>2 (100.0)</td>
<td>18 (100.0)</td>
</tr>
<tr>
<td>Amyloid PET</td>
<td>Test performed, n 9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Positive, n (%) 9 (100.0)</td>
<td>1 (100.0)</td>
<td>10 (100.0)</td>
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<td>CSF findings</td>
<td>Aβ−40 Test performed, n 1</td>
<td>0</td>
<td>1</td>
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<tr>
<td></td>
<td>Reduced, n (%) 1 (100.0)</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Aβ−42 Test performed, n 7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Reduced, n (%) 7 (100.0)</td>
<td>1 (100.0)</td>
<td>8 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Total tau Test performed, n 5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Reduced, n (%) 1 (20.0)</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td></td>
<td>p-tau Test performed, n 4</td>
<td>0</td>
<td>4</td>
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<tr>
<td></td>
<td>High, n (%) 0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Brain biopsy</td>
<td>Test performed, n 12</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>CAA observed, n (%) 12 (100.0)</td>
<td>3 (100.0)</td>
<td>15 (100.0)</td>
</tr>
</tbody>
</table>

Please see online supplemental table 1 for individual details for the cases described in this report, and online supplemental table 2 for further details of published cases to date.

*ApoE genotype reported for 18 of 20 previously published cases.

ApoE, apolipoprotein E; Aβ, amyloid-beta; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed (lobar); cSAH, convexity subarachnoid haemorrhage; cSS, cortical superficial siderosis; ICH, intracerebral haemorrhage; p-tau, phospho-tau.

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

<table>
<thead>
<tr>
<th></th>
<th>Iatrogenic cases (n=23)</th>
<th>Sporadic CAA</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first presentation</td>
<td>Mean 37.7 years</td>
<td>Associated with increasing age; rare in those under 60 years; current diagnostic criteria state age &gt;55 years</td>
<td>23 44 45</td>
</tr>
<tr>
<td>Sex</td>
<td>73.9% cases male</td>
<td>Pathologically more common in women; women more likely to have lobar ICH</td>
<td>44 46</td>
</tr>
<tr>
<td>ApoE genotype</td>
<td>ε3 present in all cases; homozygous in 66.7%</td>
<td>Usually associated with ε2 and ε4 genotypes</td>
<td>45 47</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>ICH 87.0% cases</td>
<td>Well recognised</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Recurrent ICH 65.2% cases</td>
<td>Well recognised; annual recurrence risk 7.4% (compared with 1.1% for non-CAA ICH)</td>
<td>18 46</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment 39.1% cases</td>
<td>Well recognised</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>TFNE 1 case</td>
<td>Well recognised</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Seizures 26.1% cases</td>
<td>Can occur but frequency unknown; recognised feature of CAA-related inflammation</td>
<td>18</td>
</tr>
</tbody>
</table>

ApoE, apolipoprotein E; CAA, cerebral amyloid angiopathy; ICH, intracerebral haemorrhage; TFNE, transient focal neurological episodes ("amyloid spells").
and might contribute to the cognitive features observed. Seizures are a well-recognised poststroke complication, particularly in young patients with ICH. 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 some iatrogenic cases that are atypical for sporadic CAA might be particularly epileptogenic (for example, cortical swelling). Four previously reported cases had features atypical for CAA, namely non-lobar (thalamic) ICH and lacunar infarction; these are usually attributed to deep perforator arteriopathy (also termed hypertensive arteriopathy), another common age-related cerebral small vessel disease. In none of these cases was there a reported 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 Box 1. 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. 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, and via CSF analyses; the presence of reduced CSF Aβ40 and Aβ42, with normal total tau and phospho-tau levels is particularly suggestive of CAA. 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 (real time quaking induced conversion) analyses are less reliable diagnostically. Some tests (eg, 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. 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 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

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**Box 1 Proposed diagnostic criteria for iatrogenic cerebral amyloid angiopathy (CAA)**

1. **Age of onset**
   - Symptom onset before age of 55 years (ie, below the age threshold for ‘probable’ or ‘possible’ CAA within the modified Boston criteria); 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 (ie, brain, meninges, pituitary-derived hormones); strongly suggestive
   - Relevant neurosurgical procedure (ie, 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:
       - Intracerebral haemorrhage or convexity subarachnoid haemorrhage (single or multiple)
       - Transient focal neurological episodes (‘amyloid spells’)
       - Focal seizures (with or without secondary generalisation)
       - Cognitive impairment not attributable to another cause (including acute stroke)
   - Radiological; at least one of the following:
     - CT:
       - Lobar intracerebral haemorrhage
       - Convexity subarachnoid haemorrhage
     - MRI (blood sensitive sequences; T2*-GRE, SWI)
       - Cerebral microbleeds with predominantly lobar distribution, distant from sites of parenchymal intracerebral haemorrhage
       - 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 Aβ deposition)
   - Supportive CSF features (reductions of Aβ40, Aβ42—40)
   - Brain biopsy demonstrating vascular Aβ deposition, in the absence of significant inflammation
   - Notes raised:
     - A positive amyloid-PET scan in isolation might not necessarily be specific for Aβ accumulation, depending on the tracer used; correlation with either CSF Aβ measures, brain biopsy findings and/or genetic testing for non-Aβ CAA (details below) is advised
     - Presence of significant inflammation might support an alternative diagnosis of CAA-related inflammation or Aβ related angitis (ABRA)

5. **Exclusion of genetic causes of Aβ CNS disease; this should include:**
   - Duplications of APP (including Trisomy 21, where relevant)
Box 1  Continued

\[\Rightarrow\] Mutations of APP, PSEN1, PSEN2

\[\Rightarrow\] 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 (C53T, TTR, GSN, PRNP, ITM2B) should be considered

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.

CNS, central nervous system; CSF, cerebrospinal fluid; GRE, gradient recalled echo; PET, positron emission tomography; SWI, susceptibility weighted images.

association with both of these exposures.29 Our review identified 12 cases of iatrogenic CAA following neurosurgical procedures without exposure to cadaveric material, although proper ascertaintment of this via historical records can be challenging. There is evidence from transgenic mice that Aβ can be transmitted via steel wires, and that transmission can be prevented by plasma sterilisation, but not boiling.14 There are no reported cases of iatrogenic CAA from wire from cadaveric dura mater via embolisation procedures (included two of the cases in this report, in addition to two others27) or cardiac procedures,40 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.41–43 In view of these points, and the robust experimental evidence for Aβ 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 this.

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.

Author affiliations
1MRC Prion Unit at UCL, Institute of Prion Diseases, London, UK
2Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK
3Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK
4Division of Neuropathology, National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK
5Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK
6Division of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK
7Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, UK
8Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK
9Department of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK
10Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, University College London Hospitals NHS Foundation Trust, London, UK

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