

Supplementary Material for "Iatrogenic cerebral amyloid angiopathy: an emerging clinical phenomenon"

### Supplementary Table 1

Clinical details for three cases of iCAA; pathological findings for all three cases have been reported previously<sup>1</sup>.

Case	1	2	3	
<b>CLINICAL FEATURES</b>				
Sex	Male	Female	Male	
Age at exposure (years)	3	5	4	
Estimated latency (years)	36	39	42 <sup>†</sup>	
Year of first exposure	1983	1980	1976	
Potential source(s) of exposure	DM (c)	DM (c)	NS	
ApoE genotype	ε2/ε3	ε3/ε3	ε3/ε3	
Presenting symptom	ICH	TFNE, cSAH	RPCD, ataxia, myoclonus <sup>†</sup>	
ICH	+	+	+	
Number of ICH	1	2	1	
Seizures	-	-	-	
Cognitive impairment	+	+	+	
<b>INVESTIGATIONS</b>				
MRI	cSS	-	+	ND
	CMB	+	+	ND
Amyloid PET	ND	ND	+	
CSF	Aβ-40	ND	ND	ND
	Aβ-42	ND	ND	Low
	Total tau	ND	ND	High
	p-tau	ND	ND	ND
Biopsy (including brain parenchyma)	+	+	+	
Genetic testing performed	+	+	+	
Genetics detail	APP duplication, NGS <sup>‡</sup>	APP duplication, NGS <sup>#</sup>	APP duplication, NGS <sup>#</sup>	

#### Notes:

<sup>†</sup> Presenting date and symptoms taken as onset of rapidly progressive cognitive symptoms; although this patient did have an ICH, the location was atypical for CAA, and felt on balance to be related to small vessel changes secondary to radiotherapy

<sup>‡</sup> NGS panel for genes associated with dementia, including *ABCD1*, *APP*, *ARSA*, *CCNF*, *CHCHD10*, *CHMP2B*, *CLN6*, *CSF1R*, *CTSF*, *FUS*, *GRN*, *HTRA1*, *ITM2B*, *MAPT*,

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*NOTCH3, NPC1, NPC2, PDGFB, PDGFRB, PRNP, PSEN1, PSEN2, SLC20A2, SQSTM1, TARDBP, TBK1, TREM2, TYROBP, VCP, and XPR1*

# NGS panel for genes associated with dementia, including *APP, CHMP2B, CSF1R, DNMT1, FUS, GRN, HTRA1, ITM2B, MAPT, NOTCH3, PRNP, PSEN1, PSEN2, TARDBP, TREM2, TYROBP, and VCP*

**Abbreviations:**

ApoE, apolipoprotein E; *APP*, amyloid precursor protein; CMB, cerebral microbleed (lobar); cSAH, convexity SAH; cSS, cortical superficial siderosis; DM, dura mater; DM (c), cadaveric dura mater; F, female; ICH, intracerebral haemorrhage; NGS, next generation sequencing; ND, not done ; NS, neurosurgery; RPCD, rapidly progressive cognitive decline; TFNE, transient focal neurological episodes (“amyloid spells”).

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## Supplementary Table 2

Clinical details of published cases where the diagnosis of iatrogenic CAA was made during life.

Reference	2	3	4	5			6			7	8		9	10	11	12	13			
Country	AUT	JPN	FRA	GBR	GBR	GBR	GBR	GBR	GBR	ITA	JPN	JPN	ITA	FRA	JPN	JPN	BEL	BEL	BEL	BEL
<b>CLINICAL FEATURES</b>																				
Age at first presentation (years)	38	32	46	33	36	57	48	27	34	29	30	30	51	34	37	34	32	47	31 <sup>a</sup>	32
Sex	M	M	F	F	F	F	M	M	F	M	M	M	M	M	M	M	M	M	M	M
Age at exposure (years)	NR	1	2	1	1	20	11	2 <sup>b</sup>	<1 <sup>c</sup>	1 <sup>d</sup>	<1 <sup>e</sup>	1	17	2	<1 <sup>f</sup>	<1 <sup>g</sup>	<1 <sup>c</sup>	1	1	<1 <sup>h</sup>
Estimated latency (years)	NR	31	44	32	35	37	37	25	33	28	29	28	34	32	36	33	31	46	30	31
Year of exposure	NR	NR	NR	NR	NR	NR	1980	1981	1982	1986	1982	1980	1986	1980	NR	1980	NR	NR	NR	NR
Potential source(s) of exposure	NS	NS	DM (c) NS	NS	NS	NS	DM (c) NS	DM (c)	DM (c) NS	DM NS	NS	NS	DM (c)	DM (c)	NS	DM (c) NS	NS	NS	NS	NS
ApoE genotype	ε3/ε3	ε3/ε3	ε2/ε3	ε3/ε4	ε3/ε4	ε3/ε3	ε3/ε3	ε2/ε3	ε3/ε3	ε3/ε3	ε3/ε3	ε3/ε3	ε3/ε3	ε3/ε3	ε2/ε3	ε3/ε3	ε3/ε3	NR	ε2/ε3	NR
Presenting symptom	ICH	ICH	ICH <sup>i</sup>	ICH	ICH	ICH <sup>i</sup>	SZ	SZ, ICH	ICH	ICH	SZ, cSAH	ICH	ICH	ICH	ICH	ICH	ICH <sup>i</sup>	C <sup>j</sup>	ICH	LI
ICH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-
Number of ICH	4	2	7	>2	>2	1	1	6	2	4	2	9	1	3	1	7	2	0	3	0
Seizures	-	-	-	-	-	-	+	+	+	-	+	-	-	-	+	+	-	-	-	-
Cognitive impairment	-	-	-	-	-	-	+	+	-	-	+	-	-	+	+	-	-	+	-	-
<b>INVESTIGATIONS</b>																				
MRI	cSS	NR	NR	NR	NR	NR	NR	+	+	-	NR	+	NR	NR	+	NR	+	-	+	+
	CMB	+	+	NR	NR	NR	NR	+	+	+	+	+	NR	+	+	+	+	+	+	+
Amyloid PET		NR	NR	NR	NR	NR	NR	NR	+	+	NR	+	NR	+	+	NR	NR	+	+	+
CSF	Aβ-40	NR	NR	NR	NR	NR	NR	NR	NR	NR	low	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Aβ-42	low <sup>k</sup>	NR	NR	NR	NR	NR	NR	low	low	low	low	NR	low	NR	low	NR	NR	NR	NR
	Total tau	high <sup>k</sup>	NR	NR	NR	NR	NR	NR	normal	low	normal	NR	NR	normal	NR	normal	NR	NR	NR	NR
	p-tau	NR	NR	NR	NR	NR	NR	NR	NR	low	normal	normal	NR	normal	NR	NR	NR	NR	NR	NR

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<b>Biopsy</b>	+	+	+	+	+	↓	+	+	NR	+	NR	+	NR	+	NR	+	NR	NR	+	NR	
<b>Genetic testing performed</b>	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	
<i>Genetics detail</i>	APP, PSEN1, PSEN2	n/a	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2, NGS <sup>m</sup>	APP, PSEN1, PSEN2, NGS <sup>m</sup>	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2	NGS <sup>m</sup>	NGS <sup>m</sup>	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2	APP	APP, PSEN1	APP, GSN, TTR, CST3	n/a	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2, Notch3, COL4A1 & A2	APP, PSEN1, PSEN2	APP, PSEN1, PSEN2

**Notes:**

- a Also reported in <sup>5</sup>
- b Additional procedure aged 6 years (repeat embolization, parotidectomy)
- c Aged 3 months
- d Additional neurosurgical procedure aged 21 years (cranioplasty, 2007)
- e Aged 4 months (evacuation of left subdural haematoma and right subdural hygroma); additional neurosurgical procedure at 7 months (subdural-peritoneal shunt surgery)
- f Aged 9 months
- g Aged 5 months
- h Aged < 28 days (surgery as a neonate)
- i Thalamic ICH at presentation (i.e. non-lobar ICH)
- j Later developed parkinsonism, presumed drug-induced
- k Reports describes CSF amyloid-beta and tau measurements without providing further details; assumed here to A $\beta$ -42 and total tau as these are most commonly measured

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- I CAA identified in post-mortem pathological examination of the brain
- m NGS panel for genes associated with dementia, including *APP*, *CHMP2B*, *CSF1R*, *FUS*, *GRN*, *HTRA1*, *ITM2B*, *MAPT*, *NOTCH3*, *PRNP*, *PSEN1*, *PSEN2*, *TARDBP*, *TREM2*, *TYROBP*, and *VCP* <sup>14</sup>

**Country abbreviations:**

- AUT Austria
- BEL Belgium
- FRA France
- GBR United Kingdom
- ITA Italy
- JPN Japan

**Other abbreviations:**

ApoE, apolipoprotein E; *APP*, amyloid precursor protein; CI, cognitive impairment; CMB, cerebral microbleed (lobar); cSAH, convexity SAH; cSS, cortical superficial siderosis; DM, dura mater; DM (c), cadaveric dura mater; F, female; ICH, intracerebral haemorrhage; LI, lacunar infarction; M, male; n/a, not applicable; NGS, next generation sequencing; NR, not reported ; NS, neurosurgery; *PSEN1*, presenilin 1; *PSEN2*, presenilin 2; p-tau, phospho-tau; SZ, seizure.

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