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[1].

Case		1	2	3
CLINICAL FEATURES				
Sex		Male	Female	Male
Age at exposure (years)		3	5	4
Estimated latency (years)		36	39	42†
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†
ICH		+	+	+
Number of ICH		1	2	1
Seizures		-	-	-
Cognitive impairment		+	+	+
INVESTIGATIONS				
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‡	*APP* duplication, NGS#	*APP* duplication, NGS#

Notes:

† 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

‡ 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
CLINICAL FEATURES																					
Age at first presentation (years)		38	32	46	33	36	57	48	27	34	29	30	30	51	34	37	34	32	47	31[a]	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[b]	<1[c]	1[d]	<1[e]	1	17	2	<1[f]	<1[g]	<1[c]	1	1	<1[h]
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[i]	ICH	ICH	ICH[i]	SZ	SZ, ICH	ICH	ICH	SZ, cSAH	ICH	ICH	ICH	ICH	ICH	ICH[i]	CI[j]	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		-	-	-	-	-	-	+	+	-	-	+	-	-	+	+	-	-	+	-	-
INVESTIGATIONS																					
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*	*NR*	low	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
	Aβ-42	low[k]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	low	low	low	low	*NR*	low	*NR*	low	*NR*	*NR*	*NR*	*NR*	*NR*
	Total tau	high[k]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	normal	low	normal	*NR*	*NR*	normal	*NR*	normal	*NR*	*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*	*NR*

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Biopsy	+	+	+	+	+	-[l]	+	+	*NR*	+	*NR*	+	*NR*	+	*NR*	+	*NR*	*NR*	+	*NR*
Genetic testing performed	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
Genetics detail	*APP, PSEN1, PSEN2*	*n/a*	*APP, PSEN1, PSEN2*	*APP, PSEN1, PSEN2*	*APP, PSEN1, PSEN2, NGS[m]*	*APP, PSEN1, PSEN2, NGS[m]*	*APP, PSEN1, PSEN2*	*NGS[m]*	*NGS[m]*	*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 [5]

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 Aβ-42 and total tau as these are most commonly measured

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l 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* [14]

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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