Familial British dementia: a clinical and multi-modal imaging case study

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Statements and Declarations
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Dear Sirs,

Familial British dementia (FBD) is a rare autosomal dominant dementia with features resembling Alzheimer's disease, but important differences. FBD typically first presents with memory impairment, progressing to dementia with spastic tetraparesis and cerebellar ataxia. MR imaging shows features of cerebral amyloid angiopathy and diffuse white matter disease. Longitudinal follow-up of such cases has the potential to reveal insights into the mechanisms underpinning neurodegeneration.

Here we describe a case of FBD, where the presentation with acute amnesia of presumed vascular origin, was followed by a six-year period of cognitive stability, suggesting an otherwise asymptomatic neurodegenerative disorder. We include the first description of amyloid spells in FBD, and demonstrate the accumulation of microbleeds, progressive callosal and hippocampal atrophy prior to clinical progression. We show that the pattern of amyloid PET accumulation mirrors the amyloid angiopathy present and is distinct from that seen in AD; and that despite the presence of hippocampal atrophy and known neurofibrillary tau pathology in FBD, tau PET (flortaucipir) binding was absent.

A 52-year-old, right-handed, Caucasian woman was referred for evaluation of cognitive difficulties. Aged 49 years, she awoke with a significant retrograde and anterograde amnesia following a flu-like illness. Her symptoms improved over subsequent weeks, although she was left with stable episodic memory impairment. She subsequently developed stereotyped episodes of "pixelated" central vision lasting minutes, a few times per week. She was an ex-smoker with no other significant medical history. The neurological examination was unremarkable, and she was normotensive. Neuropsychological evaluation revealed impairment of recall memory, including for autobiographical events from early adult life, with other domains intact. She remained clinically stable for the following six years although serial neuropsychology revealed slowing of processing speed and a mild decline in executive function (Table 1).

Age (years)		49	51	52	54	56	58
Verbal IQ		99	102	99	105	102	92
Performance IQ		110	110	106	113	110	78
Memory							
Recognition Memory Test Words		5-10th %	25th %	<5 %	25 %	10-25 %	<5 %
Recognition Memory Test Faces		>95 %	50 %	50-75 %	75 %	25-50 %	<5 %
Story recall	Immediate	<2 %	<2 %	<10 %	< 10 %	<1 %	2 %
	Delayed	<2 %	<2 %	<5 %	< 5 %	<1 %	<1 %
Figure recall	Immediate	2 %	<2 %	<5 %	< 5 %	10-25 %	<5 %
	Delayed	-	<10 %	<10 %	< 5 %	10-25 %	<5 %

Executive function						
Stroop	-	“High average”	78 %	60 %	52 %	20-24 %
Hayling Sentence Completion Test	-	-	“Average”	“Average”	“High Average”	“Poor”
Phonemic fluency	-	“High Average”	77-79 %	62 %	14-16 %	5 %
Processing speed (cancelling O’s)	-	-	13-14 %	4 %	21 %	4 %

Table 1: Serial neuropsychological testing between ages 49 to 58 years. A significant decline in cognitive function is observed following intracerebral haemorrhage at age 57 years.

At 57 years, she suffered a right frontal intracerebral haemorrhage causing left-sided weakness, dysarthria and a decline in cognitive functioning. Examination at age 59 years revealed spasticity in the right leg in addition to residual dysarthria and left hemiparesis (video supplement).

Brain MRI at age 52 years revealed extensive white matter hyperintensities, several lacunar infarcts, and multiple microbleeds particularly in the cerebellum, brainstem and occipital lobe, consistent with cerebral amyloid angiopathy (CAA). Imaging over the following six years demonstrated progression of white matter changes and further accumulation of microbleeds including in the frontal and temporal lobes (Figure 1). Non-linear fluid registration [1] revealed progressive volume loss initially most prominently in the corpus callosum, latterly becoming more widespread, particularly surrounding the site of previous haemorrhage. Boundary shift integral analysis [2] also demonstrated early left hippocampal atrophy with stable volumes on the right (Figure 1). Following lobar intracerebral haemorrhage, right hippocampal atrophy occurred alongside global volume loss, associated with a decline across all neuropsychological measures (Table 1).

^{18}F-flobetapir amyloid PET at age 59 years showed increased uptake in the cerebellum, brainstem, temporal, frontal and occipital cortices on visual assessment. ^{18}F-flortaucipir tau PET imaging did not show significant cortical retention, with expected off-target uptake in the basal ganglia and choroid plexus, and increased uptake at the site of the prior intracerebral haemorrhage (Figure 1).

As her father and paternal uncle had both developed dementia in their fifties, in her uncle’s case accompanied by prominent balance problems, genetic testing was arranged in a sequential fashion. Sanger sequence analysis did not reveal mutations in the PRNP, PSEN1, PSEN2, APP or NOTCH3 genes. Subsequently, next generation sequencing with Illumina Nextera Rapid Capture technology targeting a panel of dementia genes (see data supplement) was performed leading to the identification of a c.799T>A heterozygous pathogenic mutation in the integral membrane protein 2B gene (ITM2B), verified on bi-directional Sanger sequence analysis, confirming a diagnosis of familial British dementia (FBD). Following the discovery of this mutation, it was determined that she was part of the large British pedigree with ITM2B mutations.

Discussion

FBD is a rare autosomal dominant condition characterised by dementia, progressive spastic tetraparesis and cerebellar ataxia, with onset in the fifth or sixth decade [3]. Pathologically FBD is characterised by severe, widespread CAA, parenchymal amyloid plaques, and neurofibrillary degeneration, similar to sporadic Alzheimer's disease (AD) pathology.

Since the initial description of FBD in a single family by Worster-Drought in 1933, a pedigree which now spans over nine generations has been followed and clinically characterised [3]. The autosomal dominant inheritance of FBD was confirmed in 1990 through analyses of segregation and sex ratios in over 200 family members; [4] however, the underlying genetic cause was not established until 1999 when Vidal et al. identified a unique 4kD protein subunit named ABri, isolated from amyloid fibrils in a patient with FBD [5].

ABri is a fragment of a type 2 transmembrane precursor protein encoded for by the ITM2B gene (also known as BRI2) located on chromosome 13. A single base substitution at the stop codon (as found in our case) results in a longer than normal precursor protein, which, following furin-like proteolytic processing, generates an amyloidogenic peptide, ABri. This mutation was confirmed to be present in other individuals with FBD, but not in asymptomatic family members in the pedigree, individuals with other neurological disorders, or controls [5].

In vitro studies have demonstrated that ABri peptides polymerize and form amyloid-fibrils, mirroring the pathological changes seen *in vivo* [6]. The neurodegeneration in FBD has therefore been proposed to arise as a direct result of soluble oligomer toxicity [3]. More recently it has been shown that ITM2B modulates amyloid precursor protein (APP) processing, with loss of ITM2B function in FBD resulting in increased generation of amyloidogenic peptides, suggesting a common pathway between FBD and AD [7].

Unlike other forms of hereditary CAA, which are typically characterised by large cerebral haemorrhages and dementia as a result of multiple vascular events, symptomatic haemorrhage is reportedly uncommon in FBD [8]. The superficial location of intracerebral haemorrhage in this case is, however, typical of those associated with cerebral amyloid angiopathy due to preferential involvement of the cortical and meningeal vasculature [9].

Isolated episodic memory impairment is described as the most consistent early neuropsychological feature in FBD [3]. In our case, we speculate that the acute onset of amnesia, the subsequent relative stability of cognition and lack of new symptoms or signs over several years is most consistent with a thalamic vascular event, which may have then led to the identification of an otherwise asymptomatic neurodegenerative disorder. The initial MR imaging in our patient showed diffuse white matter disease, but in the absence of diffusion sequences it was not possible to confirm an ischaemic aetiology.

During the initial three years of follow-up, we observed progressive atrophy of the corpus callosum and left hippocampus. Callosal volume loss is a recognised early imaging feature in FBD [3] and is typically severe at post-mortem [10]. In patients with white matter disease, callosal atrophy has been associated with reduced processing speed and executive dysfunction [11], consistent with the serial neuropsychological testing in our case. Notably, our patient had no evidence of visuospatial deficit which could also affect performance on tests of processing speed and figure recall. The worse performance on the recognition

memory test of words compared to faces, correlates with early atrophy of the left hippocampus, a region critical for episodic verbal memory. Conversely, the stability of both verbal and performance IQ until the lobar intracerebral haemorrhage mitigates against there being significant global neurodegeneration.

Pathological descriptions of FBD have reported severe hippocampal involvement [3], although typically this is bilateral, in contrast to the initially stable right hippocampal volumes seen in our case. Early asymmetry of pathology is likely to be missed however in postmortem studies where patients typically have advanced disease. In our case, right hippocampal volume loss subsequently occurred following ipsilateral intracerebral haemorrhage. Disruption of functional networks [12] and inflammation accelerating neurodegeneration [13] may have been contributory, with ipsilateral hippocampal atrophy recognised to occur following remote ischaemic stroke [14]. Although vascular amyloid deposition is also known to contribute to cortical atrophy [15], severe hippocampal pathology has been reported in FBD unrelated to vascular involvement [3].

While prominent CAA is a core pathological feature of this disorder, the previous large case series [3] of this condition was carried out before the widespread availability of iron sensitive MR sequences and therefore emphasised the MRI white matter signal changes. We show here that FBD is associated with an extensive, and progressive microbleed burden in a predominantly occipital and infratentorial distribution, with the latter usually considered more suggestive of hypertensive microangiopathy than CAA [16]. The confluent white matter changes observed in our case are similar to those reported previosuly in FBD, typically involving the frontal and occipital periventricular regions [3]; a distribution also seen in severe hypertension, which was absent in our patient.

The episodes of pixelated vision in full consciousness are most consistent with “amyloid spells” which have not to our knowledge previously been described in FBD. Amyloid spells, also known as transient focal neurological episodes (TFNE), are recurrent, stereotyped episodes of positive and negative neurological symptoms, that typically last minutes. They frequently occur in cerebral amyloid angiopathy and are associated with a high future risk of intracerebral haemorrhage [17]. The distribution of symptoms typically correlates anatomically with CAA-related haemorrhages (including microhaemorrhages, superficial cortical siderosis and lobar intracerebral haemorrhage) and the visual symptomatology observed in our case would be consistent with the prominent occipital lobe microbleed burden. Focal seizure activity and cortical spreading depression have been proposed as underlying mechanisms for the generation of amyloid spells [17]; and anti-epileptic and migraine prophylactic medications have reportedly been effective in selected cases [18], [19]. Medication was not given in this case however, as it was not felt to be needed.

To our knowledge only one previous case of FBD has had amyloid PET imaging, revealing significant uptake of ^{11}C-PiB in the cerebellum only [20]. In our case, additional uptake was seen in the frontal, temporal and occipital cortex, mirroring areas with microhaemorrhages. Pathological studies of patients with FBD have reported neurofibrillary tangle pathology indistinguishable from that seen in AD [3] even in its phosphorylation sites [21], although the distribution and progression may differ from that seen in AD [21], noting that in the original case [10] hippocampal neurofibrillary tangles were “considerably less abundant than in Alzheimer disease”. The absence of significant ^{18}F-flortaucipir binding in this case may therefore reflect that paired helical tau pathology is minimal at this stage of the disease. Alternatively, subtle differences in tau structure might exist in FBD compared to Alzheimer’s

disease (such as the ratio of tau isoforms), which result in a lack of ^{18}F-flortaucipir binding. Finally, it was not possible to fully exclude hippocampal uptake of ^{18}F-flortaucipir due to the proximity of off-target binding in the choroid plexus.

Our case confirms that while FBD shows some clinical similarities to AD, there are notable differences, including differential patterns of amyloid PET uptake, absence of tau PET binding, the extent and distribution of white matter pathology and microbleeds, and early callosal and asymmetric hippocampal atrophy. Although rare, FBD should be considered in patients presenting with cognitive decline and imaging features of cerebral amyloid angiopathy, particularly if a family history is present. FBD may also cause acute/subacute focal symptomatology, likely reflecting vascular pathology and/or amyloid spells.

Consent to publish

The participant has consented to the submission of the case report to the journal and for publication of the supplementary videos which identify the patient.

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Figure legend

(A-E) Co-registered coronal, axial and sagittal (A) T1-weighted MRI, (B) FLAIR, (C) SWI, (D) 18F-florbetapir PET acquired on the same PET-MR scanner and (E) 18-F-flortaucipir PET images from the same year (2019). Mild cortical atrophy and areas of lacunar infarction are seen on T1 sequences. FLAIR images demonstrate confluent peri-ventricular and deep white matter changes, highlighted with overlay. SWI images show multiple microhaemorrhages and the area of previous intracerebral haemorrhage (red arrows). PET images demonstrate 18-F florbetapir uptake in the cerebellum, brainstem, and temporal lobes, with no significant cortical binding of 18-F flortaucipir. Additional 18-F florbetapir uptake in the frontal and occipital lobes is not depicted on the images above. (F) Fluid-registered T1-weighted MR images acquired on the same 3T Siemens MAGNETOM Trio scanner comparing between ages 52 and 54 years (2013-2015) show early specific contraction of the corpus callosum. (G) Fluid-registered T1-weighted images acquired on the same 3T Siemens MAGNETOM Prisma scanner between ages 56 and 58 years (2016-2018), show more widespread asymmetric volume loss. 2016-2018 structural and fluid images were aligned to the 2013-2015 images with affine registration. (H) Whole brain and ventricular volumes calculated by semi-automated methods (above left) with longitudinal boundary shift integrals (BSI) and % change for whole brain, ventricular and hippocampal volumes including tails (above right). *Acquired on the same 3T Siemens MAGNETOM Trio scanner. †Acquired on the same 3T Siemens MAGNETOM Prisma scanner

Video supplement legend

Video 1 – Patient description of symptoms of acute memory impairment and amyloid spells
Video 2 - Examination of gait demonstrates residual left hemiplegia and emergent spasticity in the right leg