THE EMERGENCE OF CAA AND ITS RELEVENCE FOR MEMORY SERVICES

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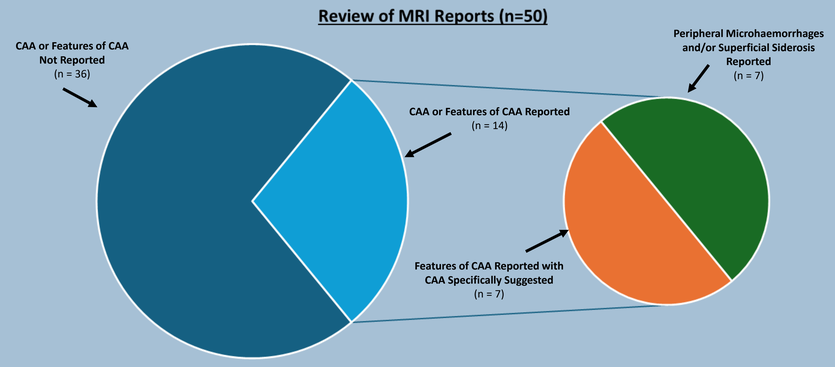
BACKGROUND

- Cerebral Amyloid Angiopathy (CAA) is a vascular disease found in >80% of confirmed Alzheimer's disease (AD) patients.
- CAA is characterized by Amyloid-β protein deposits in cerebral blood vessel walls which results in various clinical presentations including vascular rupture of fragile amyloid-β laden vessels.
- There has been a significant rise in research, diagnosis, and referrals of CAA reported over the past 5 years.
- Increasing awareness and the ability to distinguish between CAA and AD is critical for a memory service because, while they frequently coexist, they represent distinct pathological processes with different implications for patient safety, treatment eligibility, and clinical management.

REFERENCES

E. Portelius A novel pathway for amyloid precursor protein processing Neurobiol. Aging (2011)
B. Olsson CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis Lancet Neurol. (2016)
D.R. Thal Capillary cerebral amyloid angiopathy is associated with vessel occlusion and cerebral blood flow disturbances Neurobiol. Aging (2009)
J. Pannee The amyloid-beta degradation pattern in plasma--a possible tool for clinical trials in Alzheimer's disease Neurosci. Lett. (2014)
M. Rogeberg Identification of amyloid beta mid-domain fragments in human cerebrospinal fluid Biochimie (2015)
D.R. Thal Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline J. Neuropathol. Exp. Neurol. (2003)

RESULTS



- In the Cheltenham memory assessment service, features of CAA, including peripheral microhaemorrhages and superficial siderosis were reported in 28% of MRIs over the past year.
- CAA was specifically suggested in 50% of these cases.

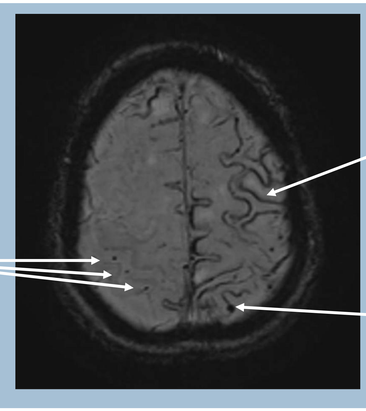
OVERLAP WITH ALZHEIMER'S DISEASE

CAA and Alzheimer's disease (AD) frequently co-occur due to their shared Amyloid- β proteinopathy and both diseases share impaired clearance through perivascular drainage pathways as a primary pathogenic mechanism. However, there are some key differences in their pathophysiology:

Feature	CAA	AD
Site of accumulation	Walls of small/medium arteries and capillaries in the cortex and leptomeninges.	Parenchymal plaques primarily in the frontal and parietal association cortices.
	A primary limitation of current amyloid-PET technology is that it detects **total amyloid burden** without distinguishing between vascular deposits (characteristic of CAA) and parenchymal plaques (characteristic of AD)	
Predominant Isoform	Primarily Aβ40—the more soluble form—which diffuses along perivascular pathways and deposits in vessel walls; its CSF levels are lower in CAA than in AD, likely due to sequestration in the vessel walls rather than clearance into the fluid.	Primarily Aβ42.
Cognitive profile	Primarily affects processing speed and executive function; memory may be relatively spared early on.	Primarily amnestic, characterized by early and severe memory deficits.
Vascular events	High risk of lobar intracerebral haemorrhage (ICH), microbleeds, and "amyloid spells" (TFNEs).	Typically lacks spontaneous lobar haemorrhages unless CAA is also present.
Neuroimaging	Predilection for the occipital and posterior lobes. MRI may show haemorrhagic markers (microbleeds, cSS) and white matter hyperintensities (WMH).	Characterized by hippocampal atrophy and cortical thinning.

FEATURES OF CAA

Single axial MRI brain – Susceptibility weighted imaging:



IMPLICATIONS ON MEMORY SERVICES

Emergence of Disease-modifying therapies

These treatments can cause Amyloid-Related Imaging Abnormalities (ARIA), such as brain swelling (ARIA-E) or bleeding (ARIA-H). Pre-existing CAA is a major risk factor for severe ARIA because these drugs may mobilize amyloid from parenchymal plaques into the already weakened vasculature. Memory services may use hemorrhage-sensitive MRI to identify CAA markers to exclude high-risk patients from these therapies.

Differing presentations

While both diseases cause cognitive decline, the nature of the impairment can differ, influencing rehabilitation needs. AD is typically characterized by amnestic deficits. In contrast, pure CAA (independent of AD) often impacts processing speed and executive function more severely, while memory may be relatively spared in early stages.

CAA also often presents with Transient Focal Neurological Episodes (TFNEs) that can be misdiagnosed as TIAs or focal seizures

Diagnostic pathway

Standard dementia workups may miss CAA. Services must use Susceptibility-Weighted Imaging (SWI) or T2*-weighted sequences to detect the microbleeds and cortical superficial siderosis that define the disease.

Management of co-morbidities

Management of common comorbidities differs if a patient has CAA. Memory services will need to be aware of the careful balance of making recommendations to optimize vascular risk factors and reduce the risk of ischemic stroke, while increasing the risk of intra-cerebral hemorrhage, which is already increased in those with CAA.

CONCLUSION

Increasing awareness of Cerebral Amyloid Angiopathy (CAA) among clinicians, including within memory services, is vital for accurate diagnosis, risk stratification and the safe implementation of emerging AD therapeutics.

CASE REPORT: TWO BROTHERS AND THE GENETICS OF FRONTO-TEMPORAL DEMENTIA

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BACKGROUND

- Fronto temporal dementia (FTD) accounts for approximately 10-20% of all dementia cases.
- The behavioural variant (bvFTD) is the most common clinical presentation, seen in approximately 50% of all autopsy-confirmed cases of FTD. bvFTD is highly heritable hence a family history is often reported. The main genes implicated are MAPT, Progranulin (GRN), and C9orf72.
- We report a case of two brothers who underwent whole genome sequencing and were found to be heterozygous for GRN-related FTD.
- Predictive genetic testing was recommended for their children, and 2 out of the 4 tested were positive for the GRN gene.

DISCUSSION

- *GRN* mutations are responsible for 20-25% of the genetic mutations in FTD, and contribute to about 10% of total FTD cases. *GRN*-FTD is inherited in an autosomal dominant pattern.
- In this case, there was no family history of FTD, although their father was diagnosed with possible undiagnosed dementia, and their mother was diagnosed with Parkinson's disease and Alzheimer's disease.
- Approximately 7% of bvFTD cases carry a genetic variant despite having no family history at all.
- This case highlights the importance of both whole genome sequencing and predictive genetic testing, even in cases with no family history of FTD.

REFERENCES

- Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. J Neurol Neurosurg Psychiatry. 2016 May;87(5):501-511
- Seelaar H, Rohrer JD, Pijnenburg YAL, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry. 2011 May;82(5):476-486
- The Association for Frontotemporal Degeneration. Case study: does it run in the family?—the genetics of FTD [Internet]. King of Prussia (PA): AFTD; 2022 Jan 5
- Williams N. Frontotemporal dementia (FTD) – what is it and how close is a cure? [Internet]. Cambridge: Alzheimer's Research UK; 2023 Oct 16.

CASE REPORT 1

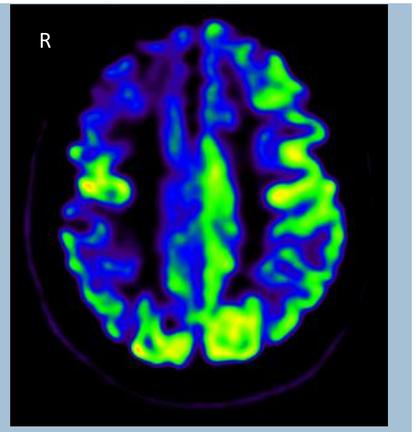
The middle brother, now aged 63, first presented with suicidal ideation and significant memory impairment, scoring 56/100 on the ACEIII. His CT head in February 2022 showed brain generalised brain atrophy

Over the following year, he developed progressive behavioural and personality changes, including loss of motivation, abandonment of self-care, emotional lability, and paranoid delusions.

His FDG PET-CT scan in March 2023 showed hypometabolism in the right frontotemporal region.

Due to escalating risk, he was later admitted to a mental health hospital in August 2023. During admission, he continued to exhibit profound behavioural disturbance with progressive functional decline.

He then underwent whole genome sequencing and was found to be heterozygous for a GRN mutation and was later discharged to a care home in August 2024.



FDG-PET: There is marked reduction of cortical uptake in the frontal lobes (right more than left) and moderate reduction of cortical uptake in both parietal lobes (more prominent on the right with involvement of the precuneus)

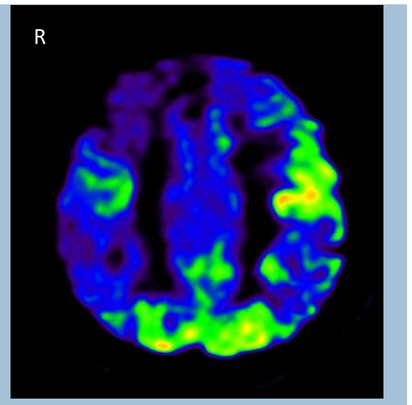
CASE REPORT 2

The oldest brother, now age 65, first presented with multiple crisis referrals for emotional distress related to a relationship breakdown and low mood. He was later referred to the memory service in September 2023 with progressive cognitive decline with marked apathy, irritability, lack of insight, difficulties with complex tasks and impaired financial planning leading to debts. He scored 24/100 on the ACEIII.

His CT head in October 2023 showed pronounced frontal and medial temporal lobe atrophy, and his FDG-PET-CT scan in February 2024 showed cortical hypometabolism in the frontal, temporal and parietal lobes.

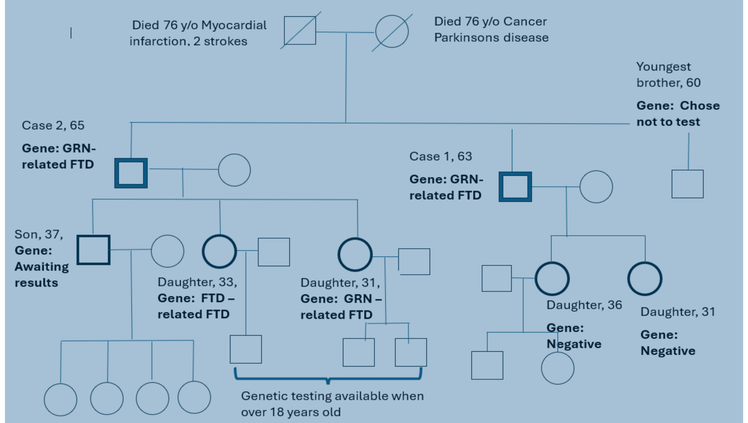
Shortly after these scans, his treating team received confirmation that his brother carried the GRN mutation, and his planned amyloid PET was cancelled, and genomic testing was prioritised. He was found to be heterozygous for a GRN mutation, confirming the diagnosis of FTD.

Since his diagnosis, his family reported a rapid deterioration in his memory and functioning, with significant risks including becoming aggressive towards family members and sexually disinhibited, and he was later admitted to the same mental health hospital that provided support for the brother.



FDG –PET: There is severe reduction of cortical uptake in the frontal lobes (right more than left) and marked reduction of cortical uptake in both parietal lobes (right more than left).

FAMILY HISTORY



GENETIC TESTING

Genetic testing is a critical diagnostic tool enabling the clinician to accurately define the pathology of the disease. It is especially important in psychiatric settings, where early bvFTD manifestations are often misdiagnosed as primary psychiatric disorders.

Identifying a *GRN* mutation is also essential for eligibility within clinical trials.

Predictive genetic testing for family members enables a risk assessment, and provides an opportunity, where relevant, to seek predictive counselling and make informed decisions as to future planning.

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