

Significant cognitive improvement with cholinesterase inhibition in AD with cerebral amyloid angiopathy

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Introduction

Cerebral amyloid angiopathy (CAA) is characterised by β -amyloid deposition in small to medium arteries, arterioles and capillaries of the cortex and leptomeninges ¹. MRI features include lobar cerebral microbleeds (best observed using iron sensitive sequences), leukoariosis, convexity subarachnoid haemorrhage, cortical superficial siderosis, and silent acute ischemic lesions, leading to the development of clinical (Boston) criteria for *in vivo* diagnosis.² CAA can present with intracranial haemorrhage, transient neurological episode (amyloid spells), rapidly progressive cognitive and neurological decline reflecting CAA related neuroinflammation, as well as more insidious cognitive impairment ³. There is considerable evidence that Alzheimer's disease (AD) and CAA are mechanistically linked: 95% of pathology proven AD have a degree of CAA pathology ⁴, ApoE4 is a risk factor for both AD and CAA ⁵ and 23% of patients with sporadic AD have imaging features of CAA⁵. Given that CAA pathology frequently accompanies AD, it may be difficult to unravel the relative contribution of each pathology in demented individuals. Whilst acetylcholinesterase inhibitors (AChEI) are widely used in AD, there is little evidence for the efficacy in patients with cognitive impairment in CAA, or in mixed disease. Here we report three patients with dementia fulfilling criteria for CAA, two with probable and one with possible AD, in whom AChEI resulted in marked cognitive improvement.

Case 1

An 81 year-old male was referred with a 3-year history of cognitive decline manifest as slowly progressive problems with episodic memory and planning. He had had a left posterior intracerebral bleed, histologically proven to be due to CAA, at the age of 64. After his stroke he was left with static problems with visual perception function, reading, writing and arithmetic. He had a subsequent haemorrhagic stroke at the age of 80 causing dysarthria and dyspraxia but he and his wife were clear that cognitive problems had emerged prior to this event and continued to worsen since. The MMSE was 11/30; formal neuropsychological evaluation showed evidence for parietal dysfunction with weak memory and executive impairment. The MRI showed significant white matter change, multiple microhaemorrhages, superficial siderosis, and atrophic hippocampi (Figure, panels A,D and G). He was diagnosed with probable CAA with supporting pathology (according to Boston criteria) and possible AD dementia (according to 2011 NIA guidelines⁶). He was commenced on Donepezil initially 5mg, latterly 10mg daily. Both he and his wife reported that this resulted in a dramatic improvement; he was able to restart playing the piano and cooking (**see supplemental video**). After four months on treatment the MMSE score had improved by 11 points to 22/30 (supplemental Table).

Case 2

A 68 year-old female with a history of ischemic heart disease presented with a 3-year history of impairments of episodic memory, navigational skills, and behavioural change. Examination revealed an MMSE score of 18/30; formal neuropsychological evaluation demonstrated impaired visual and verbal memory, impaired naming and verbal fluency and weak executive function. MR brain imaging revealed a moderate burden of vascular disease, peripheral microhaemorrhages and global atrophy

involved the hippocampi (Figure, panels B, E and H). CSF analysis revealed an elevated tau/A β 1-42 ratio (1.77) and phosphorylated tau-181 (98pg/ml, NR 0-61). She was diagnosed with Boston criteria probable CAA and probable AD (NIA high likelihood) and was commenced on Donepezil. After two months treatment, the MMSE increased by 9 points to 27/30, with significant concomitant improvements in activities of daily living. After 20 months of treatment the MMSE was 22/30.

Case 3

A 66 year old female was referred with a 6 year history of progressive problems with vision, numeracy, facial recognition and episodic memory. Examination revealed an MMSE of 20/30; formal neuropsychometry demonstrated impaired verbal memory, facial recognition and profound visuoperceptual and constructional deficits with some evidence for impaired calculation and executive function. MR brain imaging demonstrated generalised atrophy (most pronounced posteriorly), multiple cortical microhaemorrhages, particularly of the occipital lobes, and confluent white matter disease. CSF analysis revealed an elevated tau/A β 1-42 ratio (1.17) and borderline elevation of phosphorylated tau-181 (60pg/ml). She was diagnosed with Boston criteria probable CAA and probable AD (NIA high likelihood) and was commenced on Donepezil. After 4 months the MMSE had improved to 26/30. After 10 months of treatment the MMSE was 27/30.

Discussion

In AD trials individuals typically improve by 1-2 MMSE points following AchEI treatment,⁷ and so the marked cognitive (11, 9 and 6 MMSE points) and functional improvements in these three cases are striking. Most significant improvements were

in attention and language. All individuals had several years of cognitive symptoms and significant cognitive impairment by the time treatment was commenced. One explanation for the marked treatment response might be their degree of impairment: despite having moderately severe dementia, the pathological evidence of CAA and prior strokes in the first case, and presence of significant white matter changes in the second and third, meant that AD had not previously been considered, and none had been trialled on an AchEI when less severely affected. Another possibility is that the combination of CAA and AD pathology is associated with a more pronounced cholinergic deficit, predicting a greater response to AchEI treatment. These cases demonstrate the difficulties in ascribing cognitive deficits to CAA or AD pathology, and suggest that AchEI treatment should be considered in patients with CAA and cognitive decline.

Figure. MRI images for subjects 1 (Panels A,D,G), 2 (Panels B,E,H) and 3 (Panels C,F,I)

Volumetric T1 MRI showing significant hippocampal atrophy in subject 1 (A) and generalised atrophy in Subjects 2 (B) and 3 (C); T2 fluid attenuated inversion recovery (FLAIR) MRI showing established cortical stroke in subject 1 (C) and deep white matter and periventricular high signal in subjects 1 (C), 2 (D) and 3 (F). Susceptibility weighted image (SWI) MRI sequence showing peripheral microbleeds in subjects 1 (E), 2(F) and posterior microbleeds with a posterior predominance in 3(I).

Supplemental video

The individual described in case 1 and his wife describe an improvement in symptoms 3 months after starting AchEI donepezil (10mg).

Supplemental Table

Mini mental state examination scores before and after treatment with cholinesterase inhibitors.

MMSE Domain	Case	Pre-treatment	Post Treatment
Orientation (max 10)	1	4	10
	2	5	9
	3	10	10
Registration (max 3)	1	3	3
	2	3	3
	3	3	3
Attention and Calculation (max 5)	1	0	1
	2	3	5
	3	2	5
Recall (max 3)	1	1	0
	2	0	1
	3	1	2
Language (max 8)	1	3	7
	2	6	8
	3	3	6
Copying (max 1)	1	0	1
	2	1	1
	3	1	0
Total	1	11	22
	2	18	27
	3	20	26

Highlights

- CAA pathology frequently accompanies AD pathology
- CAA and AD pathology are likely to be mechanistically linked
- Individuals with AD pathology alone typically benefit from a modest cognitive improvement with AchEI (~2 MMSE points)
- We observe a striking cognitive improvement in 3 individuals with co-existing CAA and AD when treated with AchEI

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