Alzheimer's & Dementia: Translational Research & Clinical Interventions

# Cerebral amyloid angiopathy distribution in older people: a cautionary note

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# Cerebral amyloid angiopathy distribution in older people: a cautionary note

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## ABSTRACT

### INTRODUCTION

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**KEYWORDS:** Alzheimer's disease, cerebral amyloid angiopathy, amyloid PET

## INTRODUCTION

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Radioligands for Aβ are used in positron emission tomography (PET) to detect cerebral amyloid in living patients[1, 3]. Currently available Aβ-PET ligands do not discriminate amyloid plaques from CAA. Also, it has recently been recognized that Aβ-PET ligands bind to myelin with substantial affinity[4]. Thus, Aβ-PET has potential to detect white matter myelin integrity[4]. In view of the diagnostic importance placed on brain Aβ-PET, we report on the pathological distribution of CAA.

## METHODS

We examined donated frontal cerebral cortical tissue of 65 older people, derived from the UK Brains for Dementia Research network (https://bdr.alzheimersresearchuk.org/researchers/): 15 with neuropathological diagnosis of AD (age 82.9±4.76 (mean±SD) years, 8F/7M), 25 with neuropathological diagnosis of other neurodegenerative dementias (Lewy body dementia and Parkinson's disease dementia; 80.5±7.05 years, 9F/16M) and 25 without significant neurodegenerative pathology (controls; 82.0±10.2 years, 10F/15M). Formalin-fixed, paraffin-embedded sections underwent immunofluorescent labelling with well-characterised antibodies[5] specific for the C-terminal neoepitopes of Aβ40 and Aβ42. Labelled sections were examined in random order by two, independent observers (JMRF, DRH) blinded to diagnoses (For further Methods, see Supplementary file and Supplementary Figure 1).

## RESULTS

Among cases with neuropathologically-confirmed AD, a significant density of CAA was present in most cases (87% with Aβ42 positive CAA, 93% with Aβ40 positive CAA) (Figure 2). Significant density of CAA was also seen in a substantial fraction of non-AD dementia cases (34% with Aβ42 positive CAA, 51% Aβ40 positive CAA) and in control subjects (20% Aβ42, 40% Aβ40). In each group, some individuals had undetectable or very little CAA (Figure 2). Vessel Aβ40 was observed with higher density (positive vessels/cm2) in AD subjects compared to non-AD dementia subjects or controls ($p$=0.006, $p$=0.001, respectively; independent-samples Kruskal Wallis test; Figure 2). Aβ42 vessel density was also higher in AD relative to non-AD dementia or controls ($p$=0.011, $p$=0.002). Aβ-positive vessel density did not differ significantly between non-AD and control groups (Figure 2). Across all subjects there was a highly significant correlation between vessel Aβ40 and vessel Aβ42 density (Spearman's rho=0.855, $p$<0.001). Across all patient groups, CAA was undetectable or very sparse in subcortical white matter.

## DISCUSSION

These data emphasise that CAA can be abundant in non-AD and control brains. While Aβ-positive vessel density was higher in AD patients compared to non-AD or controls, CAA was by no means restricted to individuals with AD pathology. This replicates existing evidence that CAA is frequently found at autopsy in elderly individuals with or without dementia[6-9]. Conversely, we found CAA-negative individuals in each patient group including AD. This suggests that the pathological processes leading to CAA are non-identical to those causing parenchymal Aβ deposition, likely including vascular clearance pathways[10]. Our data reinforce the concept that Aβ-PET positivity may not be specific to AD. Novel PET ligands,

with pharmacological or pharmacokinetic selectivity for parenchymal vs vascular Aβ deposits[1, 3], may permit more refined patient stratification.

Our data confirm the sparseness of CAA in subcortical white matter[2]. We concur with an earlier neuropathological report that "vessels in subcortical and deep white matter were invariably spared" by CAA[2]. Aβ-PET ligands have been used by several groups as non-specific ligands for myelin and are hence biomarkers for white matter myelin density [4, 11-16]. We suggest that CAA is unlikely to confound this approach as CAA is essentially absent from subcortical white matter. On the other hand, Aβ positive CAA may be an initial or secondary histopathological pattern of AD as a result of impaired perivascular clearance (clearance pathways overloaded with amyloid, for example by mutations leading to amyloid overproduction), or inefficient amyloid transport across the blood brain barrier (e.g., by insufficient LRP1 transporter)[17-19]. Therefore, a positive amyloid PET in a patient with Aβ+ CAA may still indicate at least a risk for AD[20].

This brief report has several limitations. Notably, we do not have in-life Aβ-PET data for these cases, or details of *APOE* genotype. However, our data emphasise that caution is necessary in interpreting PET findings. CAA positivity is not specific to AD but the degree of brain Aβ-PET positivity (e.g., CAA positive density) may be a distinguishing factor between neurodegenerative diseases. Further studies are required to clarify Aβ-PET usefulness in clinical settings.

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## Figure Legends

**Figure 1. Cerebral amyloid angiopathy (CAA) positive vessels**

Examples of CAA positive vessels in a Control case (A; female, aged 88y), non-AD neurodegenerative dementia (B; Lewy body dementia) and neuropathologically defined AD (panel C). Left column shows immunolabelling for Aβ40 (red), middle column for Aβ42 (green) and rightmost column merged images for both markers. Lower magnification views in A and C show examples of density of CAA positive vessels. Scale bars 100 microns.

**Figure 2. Cerebral amyloid angiopathy (CAA) is not specific to Alzheimer's disease.**

Density of small arterial vessels positive for Aβ40 (panel A) or Aβ42 (panel B) in older people without neurodegenerative pathology (Controls), with neurodegenerative dementia other than AD (Non-AD) or with neuropathologically-confirmed AD.

**Supplementary:** Methods Supplementary file

## DISCLOSURES

None

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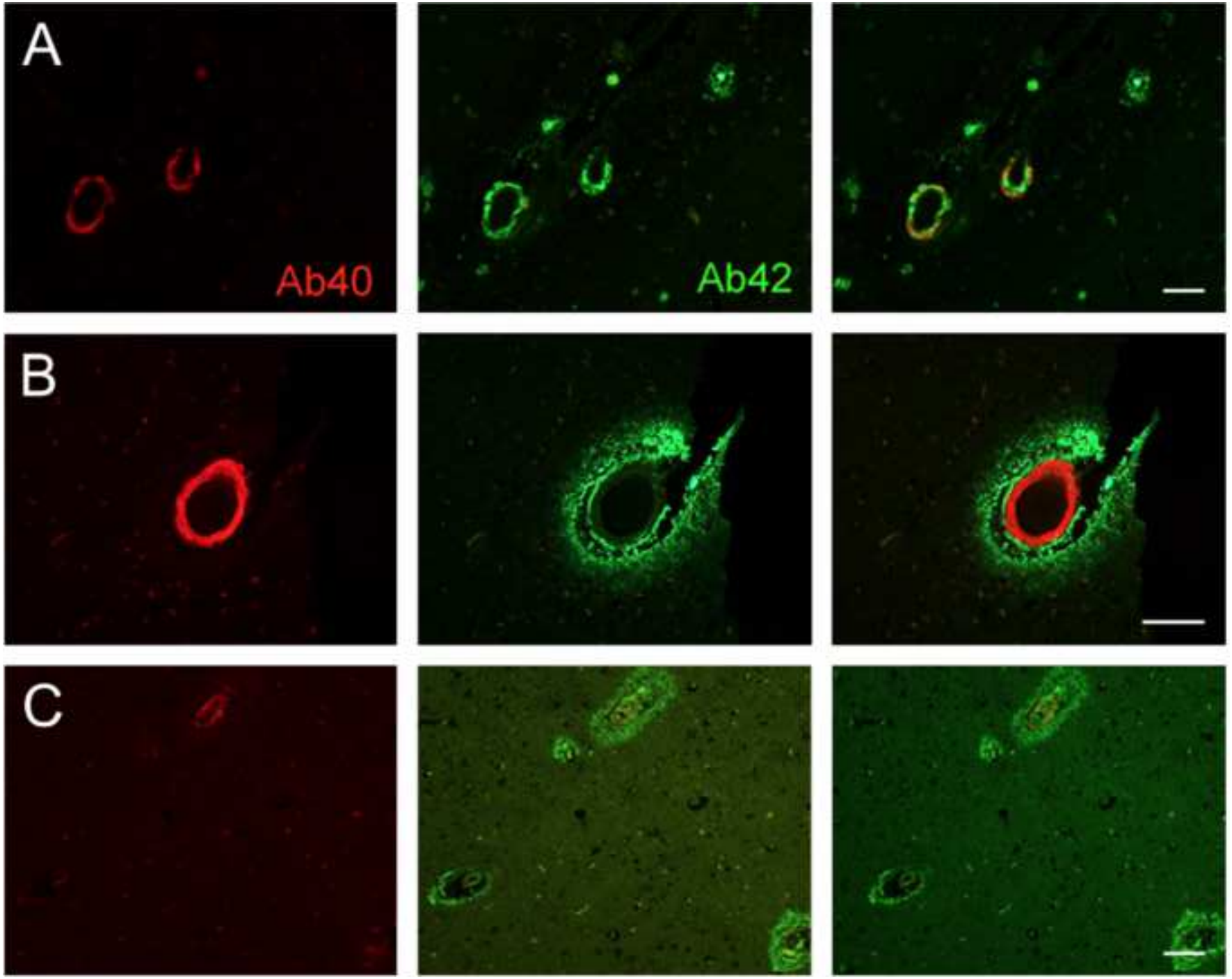

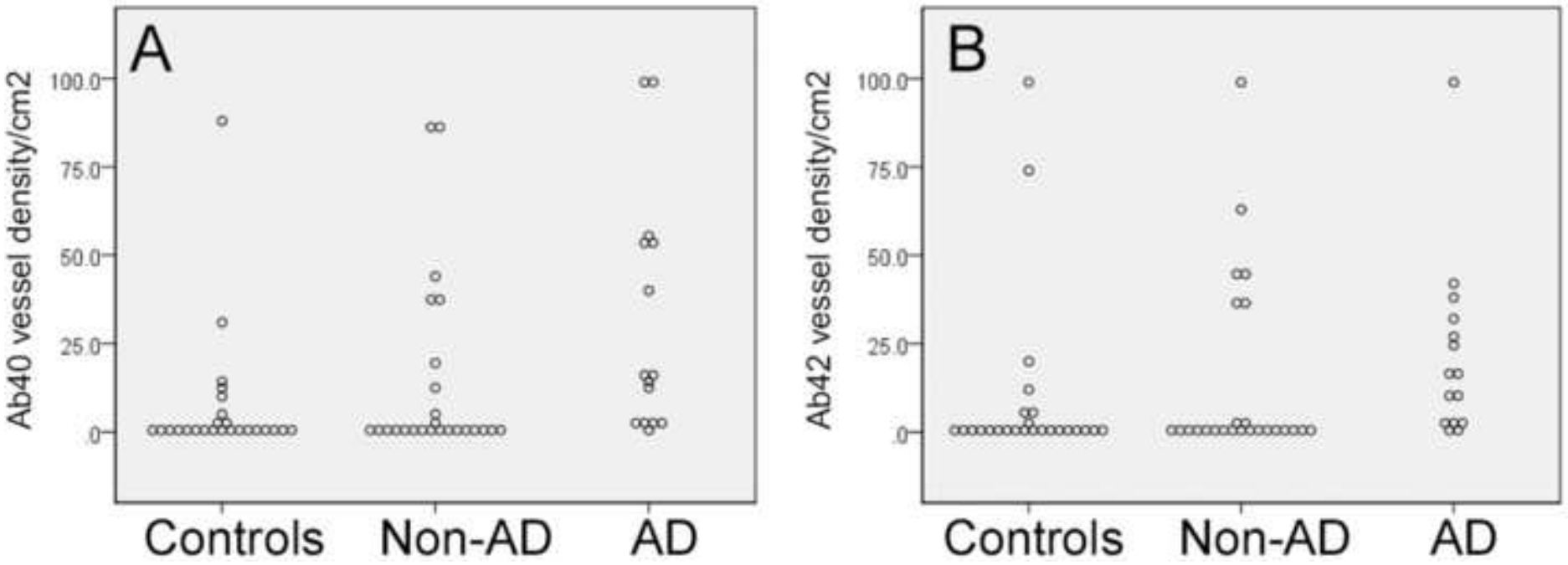

RESEARCH IN CONTEXT

1. Systematic review: Currently available amyloid positron emission tomography ligands do not discriminate cerebral amyloid plaques from amyloid angiopathy. It has recently been recognized that these ligands bind to myelin with substantial affinity.
2. Interpretation: We examined donated frontal cerebral cortical tissue of 65 older people: 15 with neuropathological diagnosis of Alzheimer's disease, 25 with neuropathological diagnosis of other neurodegenerative dementias (Lewy body dementia and Parkinson's disease dementia) and 25 without significant neurodegenerative pathology. We observed cerebral amyloid angiopathy in non-Alzheimer's disease and control brains, of comparable extent to those with neuropathologically-confirmed Alzheimer's disease. Cerebral amyloid angiopathy was absent or sparse in subcortical white matter across all patient groups. These observations support the utilisation of amyloid positron emission tomography ligands as reporters on white matter integrity.
3. Future directions: Better identification of neuropathological targets for positron emission tomography ligands.

Supplementary files