Population studies of sporadic cerebral amyloid angiopathy and dementia: a systematic review

Hannah AD Keage*1, Roxanna O Carare2, Robert P Friedland3, Paul G Ince4, Seth Love5, James A Nicoll2, Stephen B Wharton4, Roy O Weller2 and Carol Brayne1

Address: 1Department of Public Health and Primary Care, University of Cambridge, Cambridge, CB2 0SR, UK, 2Division of Clinical Neurosciences, School of Medicine, University of Southampton, Southampton, SO16 6YD, UK, 3School of Medicine, Case Western Reserve University, Cleveland, Ohio, 44106, USA, 4Academic Unit of Pathology, University of Sheffield, Sheffield, S10 2RX, UK and 5Bristol Neuroscience, University of Bristol, Bristol, BS8 1TD, UK

Email: Hannah AD Keage* - hk323@medschl.cam.ac.uk; Roxanna O Carare - R.O.Carare@soton.ac.uk; Robert P Friedland - robert.friedland@case.edu; Paul G Ince - P.G.Ince@sheffield.ac.uk; Seth Love - seth.love@bristol.ac.uk; James A Nicoll - J.Nicoll@soton.ac.uk; Stephen B Wharton - s.wharton@sheffield.ac.uk; Roy O Weller - row@soton.ac.uk; Carol Brayne - cb105@medschl.cam.ac.uk

* Corresponding author

Abstract

Background: Deposition of amyloid-β (Aβ) in vessel walls of the brain as cerebral amyloid angiopathy (CAA) could be a major factor in the pathogenesis of dementia. Here we investigate the relationship between dementia and the prevalence of CAA in older populations. We searched the literature for prospective population-based epidemiological clinicopathological studies, free of the biases of other sampling techniques, which were used as a comparison.

Methods: To identify population-based studies assessing CAA and dementia, a previous systematic review of population-based clinicopathological studies of ageing and dementia was employed. To identify selected-sample studies, PsychInfo (1806–April Week 3 2008), OVID MEDLINE (1950–April Week 2 2008) and Pubmed (searched 21 April 2008) databases were searched using the term “amyloid angiopathy”. These databases were also employed to search for any population-based studies not included in the previous systematic review. Studies were included if they reported the prevalence of CAA relative to a dementia classification (clinical or neuropathological).

Results: Four population-based studies were identified. They showed that on average 55–59% of those with dementia displayed CAA (of any severity) compared to 28–38% of the non-demented. 37–43% of the demented displayed severe CAA in contrast to 7–24% of the non-demented. There was no overlap in the range of these averages and they were less variable and lower than those reported in 38 selected sample studies (demented v non-demented: 32–100 v 0–77% regardless of severity; 0–50 v 0–11% for severe only).

Conclusion: CAA prevalence in populations is consistently higher in the demented as compared to the non-demented. This supports a significant role for CAA in the pathogenesis of dementia.
Background

Alzheimer's disease (AD) is the most common type of dementia and is characterised pathologically by the intraneuronal accumulation of neurofibrillary tangles (NFT) containing tau and ubiquitin, and by the extracellular accumulation of amyloid-β (Aβ) in brain tissue and in artery walls as cerebral amyloid angiopathy (CAA). Many studies have correlated the severity of dementia in AD with the number and distribution of NFTs, the number of plaques of insoluble Aβ, and the levels of soluble Aβ in the brain [as reviewed by [1]]. Relatively few studies, however, have investigated the relationship between dementia and the key pathological change of CAA.

CAA is the deposition of the amyloid peptides, of which Aβ is the most common, in the media and adventitia of small to medium-sized cerebral and leptomeningeal arteries, and less commonly in the walls of capillaries and veins [2-5]. The occipital lobe is most often involved, the frontal, parietal and temporal lobes less so and the cerebellum least; CAA is rare in the thalamus, basal ganglia and white matter [6,7]. Scholz [8] first emphasized the presence of CAA, suggesting that the pathological feature was associated with 'senility'. However, CAA was only reported to be a risk factor for dementia in the 1980s [9-11]. There has since then been increasing evidence to support this proposal [12,13] and CAA is now thought to play a significant role in the production of dementia [14-16]. Hereditary and sporadic types of CAA have been defined [17,18] however this review focuses on the common sporadic CAA found in the old.

The cause and effects of CAA have generated much debate especially in relation to dementia [19,20]. CAA represents the failure of elimination of Aβ along the perivascular pathways that serve as the lymphatic drainage channels for the brain [20]. Soluble tracers injected into the mouse striatum drain out of the brain along basement membranes of capillary and artery walls [21]. In CAA, Aβ is deposited in the very same perivascular drainage pathways outlined, in capillary and artery walls, in the injection studies in mice. This suggests that there is a failure of elimination of Aβ along ageing cerebral and leptomeningeal arteries [20,22,23]. Stiffening of artery walls with age and cerebrovascular disease may be a key element in reducing the elimination of Aβ from the brain in the elderly and in AD [20,24,25]. Transgenic mice that overproduce Aβ only in the brain develop CAA [19] which further supports the hypothesis that, in CAA, Aβ is entrapped in the perivascular pathways by which fluid and solutes drain from the brain [20,22]. Second: blockage of perivascular drainage pathways by Aβ may be associated with accumulation of Aβ in the brain. Ultimately it is increased levels of soluble Aβ that correlates with cognitive decline in patients with AD [28,29]. It is possible that drainage of other soluble metabolites from the brain may also be impeded in CAA. This would result in a loss of homeostasis in the neuronal extracellular environment that could contribute to cognitive decline in AD [20].

CAA has been related to other neuropathological markers of dementia including neuritic plaques and NFTs [30-32]. The amount of phospho-tau in neurites was found to be greater in grey matter surrounding cerebral vessels affected by CAA than in grey matter away from affected vessels [33]. The relationship between CAA and other neuropathologies is not simple however, and there is great heterogeneity in CAA severity in brains with AD-type pathology [34]. CAA has been reported to affect cognition/dementia status independently of other neuropathological markers of dementia [3,7,12,35,36]. However, in one study CAA was found to be associated with dementia only in those who lacked any AD-type pathology [37].

Assessing the possible impact of CAA or any neuropathological marker of dementia is best done using a sample that closely reflects the population at risk [38]. The vast majority of studies assessing the relationship between CAA and dementia have assessed selected samples (e.g., necropsy and hospital patients) which do not reflect the population at risk, in terms of either clinical or age profiles. Many of these studies have had access to limited clinical information, which further limits the interpretation of results. Thus, although CAA has been reported to play a significant role in the causation of dementia, it is unknown whether this is partly an artefact of using highly selected samples and/or the predominant use of neuropathological dementia classifications such as AD (which most likely relates to CAA closer than clinical diagnoses). The role of CAA in dementia at a population level is uncertain.

Our aim in this study was to investigate the importance of CAA in relation to dementia in a population-based context. We have addressed this by systematically reviewing previous studies that have assessed the relationship between CAA and dementia in prospectively sampled population-based cohorts of elderly people. For comparison, we have systematically reviewed studies of CAA on selected samples.

Methods

Identifying population-based studies for review

A systematic review of population-based neuropathological studies of ageing and dementia in older people was published in 2006 [39]. Six studies were identified as...
being fully population-based – the Hisayama Study (Japan), Vantaa 85+ (Finland), the Cambridge City over 75 Cohort (CC75C; England), the Honolulu-Asia Aging Study (HAAS; USA), the Cache Country Study (USA) and the MRC Cognitive Function and Ageing Study (CFAS; England and Wales). To identify articles for the current review, PsychInfo (1806–April Week 3 2008), OVID MEDLINE (1950–April Week 2 2008) and Pubmed (searched 21 April 2008) databases were used to search for papers employing any of these six study populations to assess CAA. Study titles were searched for as keywords, along with 'amyloid angiopathy'. When no study could be found using the key term 'amyloid angiopathy', it was replaced by 'neuropathology' and the relevant articles were read and searched to determine if CAA was assessed. To ensure that no further prospective population-based clinicopathological studies had been published since Zaccai et al. [39], a search was conducted using the same databases detailed above using the terms 'population' and 'amyloid angiopathy' or 'pathology'. No new studies were identified.

**Identifying selected-sample studies for review**

To compare CAA prevalence rates in population-based studies with those in studies of selected samples, we conducted a systematic review of studies in which CAA prevalence was determined relative to dementia status.

To identify studies using selected samples the PsychInfo (1806–April Week 3 2008), OVID MEDLINE (1950–April Week 2 2008) and Pubmed (searched 21 April 2008) databases were searched. One thousand three-hundred and seventy-three studies were identified using the search term 'amyloid angiopathy'. Titles and abstracts from these studies were read and studies were excluded if they did not assess human cases, the prevalence of CAA in the demented and/or non-demented specifically related to hereditary/familial CAA, reported a sample with a n less than 10, reported CAA prevalence relative to a condition other than dementia or only a feature of dementia (e.g., Parkinson's disease or APOE genotype), selected cases based on the presence of CAA, if they clearly reported the same cases as a previously selected study [e.g., [30,40,41]], if analyses were not neuropathological (e.g., MRI), or had been included as one of the population-based studies described above. The search was restricted to the English language. When a decision could not be made as to whether the article should be excluded, full articles were read. When articles were read, any cited articles that were not identified during the search were included.

**Results**

**Summary of findings from population-based studies**

Five of the six population-based studies reported CAA prevalence rates [13,14,35,42,43], of which four calculated these rates relative to dementia status (demented and/or non-demented) prior to death [all but [43]]. The findings from the four studies identified are reviewed below and summarised in Additional file 1. None of the studies assessed sex differences and only one study provided prevalence relative to age-groups [14] and thus prevalence relative to age and sex factors are not shown.

**Cambridge City over 75 Cohort (CC75C)**

Xuereb et al. [42] reported on CAA prevalence in the CC75C. The study comprised 99 individuals (68% women) over 80 years of age. CAA was assessed in meningeal and parenchymal areas of the occipital, frontal, temporal and parietal cortices as well as in the hippocampus. All CAA was recorded, regardless of severity. The authors reported that regardless of distribution, brains from participants with clinical dementia had a significantly higher prevalence of CAA (55%) than brains from participants who were not demented (26%).

**MRC Cognitive Function and Ageing Study (MRC-CFAS)**

MRC-CFAS [14] assessed the association between severe CAA and clinical dementia in 209 (57% female) individuals from England with a mean age of 86 years. Parenchymal and meningeal CAA was scored in the entorhinal, frontal, temporal, parietal and occipital cortices as well as the hippocampus. Severe CAA was present in 37% of the clinically demented and 7% of the non-demented, and was significantly associated with dementia (odds ratio/OR 9.3, 95%, confidence interval/CI 2.7–41.0) independent of other dementia-related neuropathologies.

**Honolulu-Asia Aging Study (HAAS)**

Pfeifer et al. [13] assessed CAA (controlling for other dementia-related neuropathologies) and clinical dementia in Japanese-American men in the HAAS. CAA was assessed in frontal, temporal, parietal and occipital cortices in 211 cases. Those with CAA were more likely to be older (86 versus 84 years of age) and carry at least one APOE ε4 allele (23% versus 6%) than were those without CAA. The prevalence of CAA regardless of severity did not vary significantly between the demented and non-demented, with rates of 55% and 38% respectively (significance value not provided). Accordingly, the authors concluded that CAA regardless of severity did not confer a significant risk for dementia. There was however a significant difference in the prevalence of severe CAA, with the demented having a higher prevalence (43%) than the non-demented (24%).

**Vantaa 85+ study**

Tanskanen et al. [35] assessed CAA in 74 (82% women) Finnish individuals over the age of 95 who were part of the Vantaa 85+ study. CAA severity was assessed in frontal, parietal, temporal, cingulate and cerebellar cortices, and
an average severity calculated. As reported by Pfeifer et al. [13], those with CAA were more likely to have at least one APOE ε4 allele – 45% as compared to 8%. Of the clinically demented, 59% had CAA as compared to 28% of the non-demented. It was reported that moderate or severe CAA conferred a risk for dementia (OR not reported).

From the summaries and Additional file 1 it is evident that in population-based samples, the prevalence of CAA is higher in the demented than the non-demented. On average, 55–59% of those with clinical dementia had CAA (regardless of severity) compared to 28–38% of the non-demented. For severe CAA, prevalence appeared to decrease relatively equally across demented and non-demented groups, 37–43% of the clinically demented displaying severe CAA as compared to 7–24% of the non-demented. Only one study reported the prevalence of CAA to be non-significantly higher in demented than non-demented individuals however, this was for CAA regardless of severity. When only severe CAA was assessed, those with dementia had a higher prevalence than did the non-demented [13]. This suggests that in the population, severe CAA may be a better discriminator of clinical dementia than CAA regardless of severity.

**Summary of selected-sample studies**

Thirty-eight studies were identified for review and are summarised in Additional file 2. It can be seen in Additional file 2 that the prevalence of CAA, regardless of severity, is higher in the demented (32–100% regardless of subtype or 47–100% for AD-only) than the non-demented (0–77%) in selected samples. The studies that assessed severe CAA reported prevalence rates of 0–50% in the demented (6–50% for AD-only) and 0–11% in the non-demented. Only five of the thirty-eight selected studies tested for an association between CAA and dementia [34,37,40,44,45]. All of those that did reported that cases with dementia had a significantly higher prevalence than those without, or that CAA prevalence correlated significantly with dementia. The only exception was the study by Jellinger and Attems [40] in which this was true for capillary CAA but not other forms of CAA.

**Discussion**

**How do CAA prevalences differ between population-based and selected-sample studies?**

There was greater variability in CAA prevalence rates in selected-sample studies than population-based studies. This may be due to differential bias between selected samples and the paucity of clinical information prior to death in most studies.

Estimates of CAA prevalence in the population studies were lower than in those from selected samples. This may be due to diagnostic differences (primarily neuropathological methods in studies of selected samples as compared to clinical methods in population-based studies) and younger populations being assessed, perhaps including some cases of hereditary rather sporadic CAA. Only eight studies of selected samples employed a clinical diagnosis of dementia rather than a neuropathological confirmation of AD or VaD. This is an important difference from population-based studies, all of which employed a clinical diagnosis, as neuropathological and clinical AD classification methods correspond imprecisely [46,47].

The mean age of the cohorts in selected-sample studies was between 69–91, with participants in their 40s and 50s commonly included [e.g., [44,48-50]]. These studies on selected samples therefore included much younger cases than population-based studies. Given that population-based studies most closely reflect the population at risk of disease, these findings highlight their important contribution to the understanding of pathological correlates of clinically determined dementia relevant to populations and patients. Evidence relating to the pathology of dementia needs to be obtained from both population-based as well as from selected samples.

Both the population-based studies and those on selected samples employed various stains to assess CAA, including Congo red, thioflavin-S, anti-Aβ immunohistochemistry and Weigert’s haematoxylin. Some studies used multiple stains – either different stains for different cases [e.g., [51]] or anti-Aβ immunostaining to validate Congo red-positive cases [e.g., [34]]. To the authors’ knowledge, no study has directly compared the sensitivity and specificity of these staining methods in relation to the measurement of CAA. Haglund and Englund [49] assessed a small sample (n = 10) with both Congo red and anti-Aβ immunohistochemistry. They reported that for 8 of the 10 cases, CAA severity appeared similar with both methods (Aβ immunohistochemistry perhaps giving slightly higher severity grades), while the other 2 cases showed little Congo red positivity but strong labelling of vascular Aβ.

It is not only the staining method that may produce variability between studies, the pre-treatment methods and sampling strategies also contribute [52,53]. The selection of parenchymal and/or leptomeningeal samples is also important, as CAA severity is usually higher in the latter [54]. The choice of cortical region(s) and the grading system employed in the scoring of CAA in terms of its scale (e.g., 0–3 or 0–4) and definition of severity, would have also contributed to inter-study variability.

**CAA at the population level including risk factors**

At the population level, it appears as though CAA prevalence rates are consistently higher in the demented than the non-demented, suggesting that CAA is an important
dementia-related abnormality in a population context, particularly severe CAA. This finding is pertinent in light of recent reports of overlap in the prevalence rates between demented and non-demented cohorts of other dementia-related abnormalities such as plaques and tangles [14,47].

Determination of the presence and severity of CAA may aid in neuropathological assessment that more closely resembles the clinical assessment of dementia. The MRC-CFAS study reported the OR for risk of a clinical dementia diagnosis to be higher for severe CAA (OR = 9.3, 95%CI 2.7–41.0) than either neocortical neuritic plaques (OR = 5.0, 95%CI 1.2–29.8) or neocortical tangles (OR = 4.6, 95%CI 1.5–15.8) [14]. Future work should elucidate whether the inclusion of CAA in the neuropathological assessments of dementias such as AD improves the specificity and sensitivity of classification relative to clinical dementia during life. Further, given that CAA is a potential discriminator of dementia from normal ageing, imaging methods that detect CAA in living individuals may aid in the differential diagnosis of clinical dementia syndromes [5,12,55]. CAA is a potential predictor of the development of dementia during life, for which treatment and management strategies might be developed. The presence of CAA in the living non-demented may also indicate a specific syndrome such as Vascular Cognitive Impairment No-Dementia (VCI-ND) [56] – this also needs to be investigated in the future.

Some studies [6,34,43,57-60] but not all [14,48,61] have found that increasing age in the elderly is a risk factor for CAA. In a community sample of 100 individuals 50–91 years, Mastaglia et al. [62] found CAA prevalence to increase with age to a maximum in those over 90. As yet there is no evidence that the prevalence of CAA varies with sex [7,43]. Cerebrovascular disease (e.g., atherosclerosis) is another possible risk factor for CAA. It has been suggested to affect the efficiency of Aβ removal by perivascular drainage, leading to CAA [63]. However, hypertension, diabetes mellitus and hyperlipidemia do not appear to be risk factors for CAA [60].

The ε4 allele of the APOE gene has been reported to be a risk factor for CAA as it is for AD [64-68] and this was seen in two of the population-based studies reviewed here [13,35]. It has been suggested that the association between the APOE ε4 allele and CAA is due to the ε4 allele being related to vascular rather than parenchymal accumulation of Aβ [64]. The APOE ε4/ε4 genotype has been associated with CAA-related inflammation [69], while the ε2 allele has been reported to be a risk factor for CAA-related haemorrhage in both those with and those without AD [65,70].

How clinical studies can inform these findings
Studies of clinic and/or necropsy cohorts are valuable for determining the implications of CAA at a population level. For instance, these studies have found that many neurological events induced by CAA can themselves compromise neurological integrity and cognitive function. For example, CAA increases vessel wall fragility and increases the risk of cortical and subcortical intracerebral haemorrhage [5,71], carrying a high risk of poor neurological and cognitive outcome [72]. CAA may impair blood flow, leading to ischemic damage to the cerebral cortex and white matter, which is also associated with neurological and cognitive impairment [73-75]. CAA is associated with failure of drainage of interstitial fluid from cerebral white matter in AD and the pathogenesis of leukoaraiosis [76]. Further, the Aβ peptide that accumulates in CAA can provoke inflammation/vasculitis in a small subset of individuals [69,77] with both microglia and T-cells involved [78]. CAA-related inflammation has also been proposed to be related to severe cognitive decline due to circulatory dysfunction [69,78]. Thus, patients who develop haemorrhage, ischaemia, white matter damage or inflammation as complications of CAA are at risk of further cognitive impairment.

The type of vessel involved and distribution of CAA may differentially affect cognition. It was reported that capillary CAA is more closely associated with impaired cognition than is CAA of larger blood vessels [30,79]. Further, although CAA is most prevalent in the posterior regions of the cerebral hemispheres, the association between CAA and clinical dementia has been reported to be strongest for frontal CAA [37].

Possible limitations and future directions
The four population-based studies reviewed here employed relatively crude measures of CAA. There were varying attempts to take into account the interactions with a wide range of other dementia-related pathologies and the severity of CAA. No study took into account the distribution of CAA, the presence of inflammation and the type of vessel affected. All these factors have been reported to influence the association with cognition [e.g., 30,37,79,80].

Population-based studies, as with studies on selected samples, face some important stumbling blocks in the investigation of CAA. The distribution of CAA is variable [4] and its detection critically dependent of the extent and distribution of histological sampling. There is likely to be an under-diagnosis of CAA even in severe cases [18]. There is currently no diagnosis of CAA even in severe cases [18]. There is currently no consensus as to how to sample for or detect CAA or grade its severity. Full evaluation of CAA is most satisfactorily assessed by isolating cerebral and leptome-
ningeval vessels from the brain and staining for amyloid with Thioflavin [22,76]. A standard consensus method for detecting and classifying CAA would greatly facilitate future population-based multi-centre studies of CAA and such plans are underway.

Conclusion
CAA prevalence rates are higher in demented than non-demented old people in prospective population-based studies. This suggests that CAA is a more significant dementia-related abnormality than previously recognised and underscores the need to understand the aetiology and pathogenesis of CAA and its contribution to dementia in the population.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors drafted and edited the manuscript, HADK also carried out the systematic review.

Additional material

Additional file 1
Additional table 1. Prevalence (to nearest whole number) of CAA in population-based studies regardless of severity and relative to severe CAA only in the demented and non-demented, as well as the significance of association between CAA and clinical dementia.
Click here for file

Additional file 2
Additional table 2. Prevalence (to nearest whole number) of CAA in studies using selected non-population-based samples in the demented and non-demented, as well as the significance of association between CAA and clinical dementia (if given) ordered by date of publication.
Click here for file

Acknowledgements
HADK is supported by a BUPA Foundation grant (RHAG/094).

References
1. Lowe J, Mirra S, Hyman B, Dickson D: Ageing and Dementia. In Greenfield's Neuropathology 8th edition. Edited by: Love S, Ellison D. London: Hodder Arnold; 2008:1031-1152.
2. Revesz T, Ghiso J, Lashley T, Plant G, Rostagno A, Frangione B, Bolton JL: Cerebral amyloid angiopathies: a pathologic, biochemical, and genetic view. J Neuropathol Exp Neurol 2003, 62(9):885-898.
3. Zekry D, Duycyaerts C, Belmin J, Geoffre C, Moulias R, Hauw JJ: Cerebral amyloid angiopathy in the elderly: vessel walls changes and relationship with dementia. Acta Neuropathol 2003, 106(4):367-373.
4. Vinters HV: Cerebral amyloid angiopathy, A critical review. Stroke 1987, 18(2):311-324.
5. Salat DH, Smith EE, Tuch DS, Benner T, Pappu V, Schwab KM, Gurrol ME, Rosas HD, Rosand J, Greenberg SM: White matter alterations in cerebral amyloid angiopathy measured by diffusion tensor imaging. Stroke 2006, 37(7):1759-1764.
6. Vinters HV, Gilbert JJ: Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. Stroke 1983, 14(6):924-928.
7. Xu D, Yang C, Wang L: Cerebral amyloid angiopathy in aged Chinese: a clinico-neuropathological study. Acta Neuropathol 2003, 106(1):89-91.
8. Schols W: Studien zur Pathologie der Hirngefäße II. Die drusige Entartung der Hirnarterien und -capillaren. (Eine Form seniler Gefäßveränderung). Zeitschrift für die gesamte Neurologie und Psychiatrie 1938, 162:694-715.
9. Coria F, Castano EM, Frangione B: Brain amyloid in normal aging and cerebral amyloid angiopathy is antigenically related to Alzheimer's disease beta-protein. Am J Pathol 1987, 129(5):422-428.
10. Glenner GG: Amyloid deposits and amyloidosis: the beta-fibrilloses (second of two parts). N Engl J Med 1980, 302(24):1333-1343.
11. Glenner GG: Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med 1980, 302(23):1283-1292.
12. Greenberg SM, Gurrol ME, Rosand J, Smith EE: Amyloid angiopathy-related vascular cognitive impairment. Stroke 2004, 35(11 suppl 1):2616-2619.
13. Pfeifer LA, White LR, Ross GW, Petrovitch H, Launer LJ: Cerebral amyloid angiopathy and cognitive function: the HAAS autopsy study. Neurology 2002, 58(11):1629-1634.
14. MRC-CFAS: Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet 2001, 357(9251):169-175.
15. Greenberg SM: Cerebral amyloid angiopathy and dementia: Two amyloids are worse than one. 2002:1587-1588.
16. Weller RO, Nicoll JA: Cerebral amyloid angiopathy: pathogenesis and effects on the ageing and Alzheimer brain. Neuro Res 2003, 25(6):611-616.
17. Haan J, Roos RA: Comparison between the Icelandic and Dutch forms of hereditary cerebral amyloid angiopathy. Clin Neurol Neurosurg 1992, 94(suppl):S82-83.
18. Astens J: Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. Acta Neuropathol 2003, 110(4):345-359.
19. Herzog IC, van Nostrand WE, Jucker M: Mechanism of cerebral beta-amyloid angiopathy: murine and cellular models. Brain Pathol 2006, 16(1):40-54.
20. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO: Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer’s disease. Brain Pathol 2008, 18(2):253-266.
21. Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JA, Perry VH, Weller RO: Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol Appl Neurobiol 2008, 34(2):131-144.
22. Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Rohrer AE: Cerebral amyloid angiopathy: amyloid beta accumulates in perivascular interstitial fluid drainage pathways in Alzheimer’s disease. Am J Pathol 1998, 153(3):723-733.
23. Preston SD, Steart PV, Wilkinson A, Nicoll JA, Weller RO: Capillary and arterial cerebral amyloid angiopathy in Alzheimer’s disease: defining the perivascular route for the elimination of amyloid beta from the human brain. Neuropathol Appl Neurobiol 2003, 29(2):106-117.
24. Weller RO, Cohen NR, Nicoll JA: Cerebrovascular disease and the pathophysiology of Alzheimer’s disease. Implications for therapy. Panminerva Med 2004, 46(4):239-251.
25. Schley D, Carare-Nnadi R, Please CP, Perry VH, Weller RO: Mechanisms to explain the reverse perivascular transport of solutes out of the brain. J Theor Biol 2006, 238(4):962-974.
26. McCarroll MO, Nicoll JA, Stewart J, Ironside JW, Mann DM, Love S, Graham DI, Dewar D: The apolipoprotein E epsilon2 allele and...
the pathological features in cerebral amyloid angiopathy-related hemorrhage. J Neuropathol Exp Neurol 1999, 58(7):711-718.

27. Zhang-Nunes SX, Maat-Schiamen ML, van Duijn SG, Roos RA, Frosh MP, Greenberg SM: The cerebral beta-amyloid angiopathies: hereditary and sporadic. Brain Pathol 2006, 16(1):30-39.

28. Lue LF, Kuo YM, Roher AE, Brachova L, Shen Y, Sue L, Beach T, Kurth JH, Rydel RE, Rogers J: Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer’s disease. Ann J Pathol 1999, 155(3):853-862.

29. McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, Bush AI, Masters CL: Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer’s disease. Ann Neurol 1999, 46(6):860-866.

30. Attems J, Jellinger KA: Only cerebral capillary amyloid angiopathy correlates with Alzheimer pathology – a pilot study. Acta Neuropathol 2004, 107(2):83-90.

31. Ellis RJ, Olichney JM, Thal LJ: Cerebral amyloid angiopathy in Alzheimer’s disease. Neurology 1975, 25(2):120-126.

32. Gandy S: The role of cerebral amyloid beta accumulation in common forms of Alzheimer’s disease. J Clin Invest 2005, 115(5):1121-1129.

33. Timofeeva M, Vonsattel J-P, Wilcock GK, Love S: Relationship of neurofilbrillary pathology to cerebral amyloid angiopathy in Alzheimer’s disease. Neurobiol Appl Neuropat 2005, 31(4):414-421.

34. Yamada M: Risk factors for cerebral amyloid angiopathy in the elderly. Ann N Y Acad Sci 2002, 977:37-44.

35. Tanskanen M, Lindsberg PJ, Tiainen PJ, Polvikoski T, Sulkava R, Verkkoniemi A, Rastas S, Paetau A, Kiuru-Enari S: Cerebral amyloid angiopathy in a 95+ cohort: complement activation and apolipoprotein E (ApoE) genotype. Neuropathol Appl Neuropat 2005, 31(6):589-598.

36. Tian J, Shi J, Mann DM: Cerebral amyloid angiopathy and dementia. Pannminerva Med 2004, 46(4):253-264.

37. Attems J, Quass M, Jellinger KA, Lintner F: Topographical distribution of cerebral amyloid angiopathy and its effect on cognitive decline are influenced by Alzheimer disease pathology. J Neurol Sci 2007, 257(1-2):49-55.

38. Schoenmaker N, van Gool WA: The age gap between patients in clinical studies and in the general population: a pitfall for Alzheimer study design. Acta Neurol Scand 2004, 110(1):62-63.

39. Zaccia J, Ince P, Brayne C: Population-based neuropathological studies of dementia: design, methods and areas of investigation – a systematic review. BMC Neurology 2006, 6:2.

40. Jellinger KA, Attems J: Prevalence and impact of cerebrovascular pathology in Alzheimer’s disease and parkinsonism. Acta Neurol Scand 2006, 114(1):38-46.

41. Jellinger KA, Attems J: Prevalence and pathogenic role of cerebrovascular lesions in Alzheimer’s disease. J Neurol Sci 2005, 239-240:37-47.

42. Xuerub JH, Brayne C, Dufoull C, Gerza H, Witschik C, Harrington C, Mukaetova-Ladinska E, McGee MA, O’Sullivan A, O’Connor D, et al.: Neuropathological findings in the very old. Results from the first 101 brains of a population-based longitudinal study of dementing disorders. Ann N Y Acad Sci 2000, 903:490-496.

43. Masuda J, Tanaka K, Ueda K, Omae T: Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. Stroke 1988, 19(2):205-210.

44. Bergeron C, Ranalli PJ, Miceli PN: Amyloid angiopathy in Alzheimer’s disease. Can J Neurol Sci 1987, 14(4):564-569.

45. Soininen H, Larson EB, Crane PK, Hanesse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ: Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007, 62(4):406-413.

46. Gauthier S, Mintun MA, Hedreen JC, Sueni SM, Hanson LA, Heyman A: The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD), Part X. Neuropathology Confirmation of the Clinical Diagnosis of Alzheimer’s Disease. Neurology 1995, 45(3):461-466.

47. Polvikoski T, Sulkava R, Myllykangas L, Notsola IL, Niinisto L, Verkkoniemi A, Kainulainen K, Kontula K, Perez-Tur J, Hardy J, et al.: Prevalence of Alzheimer’s disease in very elderly people: a prospective neuropathological study. Neurology 2001, 56(12):1690-1696.

48. Esiri MM, Wilcock GK: Cerebral amyloid angiopathy in dementia and old age. 1986:1221-1226.

49. Hulihan M, England B: Cerebral amyloid angiopathy, white matter lesions and Alzheimer encephalopathy – a histopathological assessment. Dement Geriatr Cogn Disord 2002, 14(3):161-166.

50. Vogelgesang S, Warzok RW, Caspari I, Kunert-Keil C, Schroeder E, Kroemer HK, Siegmond W, Walker LC, Pahnke J: The role of P-glycoprotein in cerebral amyloid angiopathy; implications for the early pathogenesis of Alzheimer’s disease. Curr Alzheimer Res 2004, 1(2):121-125.

51. Ellis RP, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, Heyman A: Cerebral amyloid angiopathy in the brains of patients with Alzheimer’s disease: the CERAD experience, Part XV. Neurology 1996, 46(6):1592-1596.

52. Alafuzoff I, Pikkainen M, Arzberger T, Thal DR, Al-Sarraj S, Bell J, Bodi I, Budka H, Capetillo-Zarate E, Ferrer I, et al.: Inter-laboratory comparison of neuropathological assessments of beta-amyloid protein: a study of the BrainNet Europe consortium. Acta Neuropathol 2008, 115(5):533-546.

53. Bely M, Malovcovitzky J: Sensitivity and specificity of Congo red staining according to Romhanyi. Comparison with Puchter’s and Bennett’s Bennett’s methods. Acta Neuropathol 1999, 108(1):39-45.

54. Greenberg SM, Vonsattel J-PG: Diagnosis of Cerebral Amyloid Angiopathy: Sensitivity and Specificity of Cortical Biopsy. Stroke 1997, 28(7):1418-1422.

55. Knudsen KA, Rosand J, Karluk D, Greenberg SM: Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston Criteria. Neurology 2001, 56(4):537-539.

56. Moorhouse P, Rockwood K: Vascular cognitive impairment: current concepts and clinical developments. The Lancet Neurology 2008, 7(3):246-253.

57. Hart MN, Merz P, Bennett-Gray J, Menezes AH, Goeken JA, Schelper RL, Wisniewski HM: Beta-amyloid protein of Alzheimer’s disease is found in cerebral and spinal cord vascular malformations. Am J Pathol 1988, 132(1):167-172.

58. Love S, Nicoll JA, Hughes A, Wilcock GK: APOE and cerebral amyloid angiopathy in the elderly. Neuroreport 2003, 14(11):1535-1536.

59. Tomonaga M: Cerebral amyloid angiopathy in the elderly. J Am Geriatr Soc 1981, 29(4):151-157.

60. Yamada M, Tsukagoshi H, Chupinno E, Hayakawa M: Cerebral amyloid angiopathy in the aged. J Neurol 1987, 214(6):371-376.

61. Mountjoy CQ, Tomlinson BE, Gibson PH: Amyloid and senile plaques and cerebral blood vessels. A semi-quantitative investigation of a possible relationship. J Neurol Sci 1982, 61(1):23-31.

62. Mastaglia FL, Byrnes ML, Johnsen RD, Kakulas BA: Prevalence of cerebral vascular amyloid-beta deposition and stroke in an ageing Australian population: a postmortem study. J Clin Neurosci 2003, 10(2):186-189.

63. Weiler RO, Trow HY, Preston SD, Mazanti I, Nicoll JA: Cerebrovascular disease is a major factor in the failure of elimination of Abeta from the aging human brain: implications for therapy of Alzheimer’s disease. Ann N Y Acad Sci 2002, 977:162-168.

64. Chalmers K, Wilcock GK, Love S: APOE epsilon 4 influences the pathological phenotype of Alzheimer’s disease by favouring cerebrovascular over parenchymal accumulation of a beta protein. Neuropathol Appl Neurobiol 2003, 29(3):231-238.

65. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT: Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol 1995, 38(3):254-259.

66. McCarron NO, Nicoll JA: Apolipoprotein E genotype and cerebral angiopathy-related hemorrhage. Ann N Y Acad Sci 2000, 903:176-179.

67. Kassemman DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN: Apolipoprotein E epsilon 4 influences the pathological phenotype of Alzheimer’s disease by favouring cerebrovascular over parenchymal accumulation of a beta protein. Neuropathol Appl Neurobiol 2003, 29(3):231-238.

68. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM: Clinical manifestations of cerebral amyloid angiopathy-related inflammation. Ann Neurol 2004, 55(2):250-256.
70. Nicoll JA, Burnett C, Love S, Graham DI, Ironside JW, Vinters HV: High frequency of apolipoprotein E epsilon 2 in patients with cerebral vascular disease: relationship to cerebral amyloid angiopathy. Ann Neurol 1996, 39(5):682-683.

71. Tian J, Shi J, Bailey K, Mann DM: Relationships between arteriosclerosis, cerebral amyloid angiopathy and myelin loss from cerebral cortical white matter in Alzheimer's disease. Neurobiol Aging 2004, 30(1):46-56.

72. Tatemichi TK, Desmond DW, Mayeux R, Paik M, Stern Y, Sano M, Remien RH, Williams JBW, Mohr JP, Hauser WA, et al.: Dementia after stroke: Baseline frequency, risks, and clinical features in a hospitalized cohort. Neurology 1992, 42(6):1185.

73. Fernando MS, Ince PG: Vascular pathologies and cognition in a population-based cohort of elderly people. J Neurol Sci 2004, 226(1-2):13-17.

74. Jellinger KA: The pathology of ischemic-vascular dementia: an update. J Neurol Sci 2002, 203-204:153-157.

75. Jellinger KA: Cognitive impairment and cellular/vascular changes in the cerebral white matter. Ann NY Acad Sci 1997, 826:92-102.

76. Roher AE, Kuo YM, Esh C, Sano M, Remien RH, Williams JBW, Mohr JP, Hauser WA, et al.: Cerebral amyloid angiopathy: an autopsy study. J Neurol Sci 2003, 214(1-2):50-515.

77. Greenberg SM, Bacskai BJ, Hyman BT: Alzheimer disease's double-edged vaccine. Nat Med 2003, 9(4):389-390.

78. Jellinger KA: Alzheimer disease and cerebrovascular pathology in Alzheimer's disease. Mol Med 2003, 9(3-4):112-122.

79. Sjogren SM, Bacsai BJ, Hyman BT: Alzheimer disease's double-edged vaccine. Nat Med 2003, 9(4):389-390.

80. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD: Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 2003, 62(12):1287-1301.

81. Jellinger K: Cerebrovascular amyloidosis with cerebral hemorrhage. J Neurol 1977, 214(3):195-206.

82. Glenner GG, Henry JH, Fujihara S: Congophilic angiopathy in the pathogenesis of Alzheimer's degeneration. Ann Pathol 1981, 1(2):10-20.

83. Joachim CL, Morris JH, Selkoe DJ: Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. Ann Neurol 1988, 24(1):50-56.

84. Dickson DW, Crystal HA, Mattiace LA, Masur DM, Blau AD, Davies P, Yen SH, Aronson MK: The identity of normal and pathologic cerebral amyloid angiopathy in Alzheimer's disease. Arch Neurol 1995, 52(7):831-836.

85. Lopez OL, Claassen D: Cerebral amyloid angiopathy: an autopsy study. J Neuropathol Exp Neurol 2008, 67(1):102-113.

86. Olichney JM, Hansen LA, Hofstetter CR, Grundman M, Katzman R, Thal LJ: Cerebral infarction in Alzheimer's disease is associated with severe amyloid angiopathy and hypertension. Arch Neurol 1995, 52(7):702-708.

87. Chalmers K, Wilcock G, Love S: Contributors to white matter damage in the frontal lobe in Alzheimer's disease. Neurobiol Aging 2008, 13(6):623-631.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2377/9/3/prepub