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EDITORIAL

# Cerebrovascular pathology: the dark side of neurodegeneration

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It is widely recognised that cerebrovascular disorders contribute to the burden of physical morbidity and mortality in a major way. More profoundly, injury or ageing-related structural and functional disturbances in the macro- or microcirculation of the brain make it vulnerable to cognitive dysfunction and change in behaviour. Although cause and effect are not completely understood, it is apparent that cerebral hypoperfusion and impaired drainage of interstitial fluid and soluble metabolites are recurrent themes during brain ageing. The cluster on cerebrovascular disorders in this issue of *Acta Neuropathologica* focuses on pathophysiological mechanisms associated with brain ageing and dementia, particularly Alzheimer's disease, bringing together the latest results, novel angles and working hypotheses. The following articles advance our knowledge of the clinical, diagnostic, imaging and physiological aspects as they relate to the neuropathology of cerebrovascular disorders and Alzheimer's disease.

Arteries of the brain can be regarded as encompassing two major functions: first, the vital function of delivering blood together with oxygen, glucose and nutrients to the brain; second, the elimination of interstitial fluid and solutes such as amyloid-beta (Aβ), along intramural perivascular pathways. Both these functions progressively fail with age and are particularly severely affected in Alzheimer's disease and related dementias. To explain these failures, the concept of protein elimination failure angiopathy (PEFA) has been devised [1]. PEFA incorporates mechanisms involved in the pathogenesis of a spectrum of disorders that exhibit both unique and common features of protein accumulation in blood vessel walls. However, the anatomical pathways for the lymphatic drainage of the brain and for the convective influx/glymphatic pathways of communication between the cerebrospinal fluid and the brain parenchyma are constantly being more exactly defined. In this issue, Morris et al. [8] emphasise the critical role played by basement membranes in guiding fluid and solutes in and out of the brain and how these essential pathways follow different routes associated with cerebral arteries. The findings convey an alternative concept of intramural and extramural perivascular transport. Such transport pathways do not involve perivascular spaces but rather rely for their appropriate physiological functions upon highly controlled basement membrane pathways.

In the article by *Love and Miners* [4], there is a strong proposal that cerebral hypoperfusion is an early event in Alzheimer's disease that involves non-structural vascular dysfunction rather than structural abnormalities in blood vessel walls. Their refreshing review highlights vasoconstriction in strategic areas of the brain, including the deep white matter, as a key problem in the pathophysiology of Alzheimer's disease. One major contributor is the vasoconstrictor endothelin-1 (EDN-1), which is not only produced by endothelial cells but also other cells. Pharmacotherapy targeting relevant biochemical pathways, in particular the use of selective EDN1 receptor antagonists may be effective in slowing down progression of dementia by improving cerebral perfusion and reducing permeability of the blood–brain barrier.

Merlini et al. [5] provide evidence from examination of postmortem brain tissue with mild AD pathology to propose that the loss of vascular smooth muscle and

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degradation of arterial elastin is related to tau pathology and starts during early Braak staging (II–III). The arterial remodelling impairs arterial wall distension dynamics driving perivascular drainage and decreasing the aortic blood propulsion wave cushioning capacity, which increases the distension and shear stress on the downstream, fragile arteriolar and capillary walls. They further suggest that microvessel wall stress leads to pathologic arteriolar and capillary remodelling and ultimately, contributes to cerebral amyloid angiopathy and Alzheimer's disease-related microvascular pathology.

It is clear that imaging of the living brain has been greatly refined with progressive improvement in the resolution of scans during the last decade. Techniques currently used to study both structure and function such as computerised axial tomography, magnetic resonance imaging and positron emission tomography have profoundly increased our understanding of the mechanisms of cerebrovascular dysfunction. As discussed by Montagne et al. [6], advances in brain imaging techniques have enabled region-specific quantification using various markers and tracers and have allowed clinical features of cognitive impairment to be correlated with cerebral metabolism, Aβ burden and tissue changes such as enlarged perivascular spaces and white matter abnormalities. With focus on Alzheimer's disease again, the authors suggest that impairment in both vasoreactivity and blood–brain barrier function is central to the aetiology of Alzheimer's disease.

We have known that the ε4 allele of the apolipoprotein E gene (APOE: gene, apoE: protein) is the strongest susceptibility factor for Alzheimer's disease for over two decades. Mystery still surrounds how *APOE* modulates the pathogenesis of Alzheimer's disease. In their review, Tai et al. [9], discuss current evidence for how *APOE* genotypes differentially modulate the function of the cerebrovasculature, with apoE and its receptors differentially expressed in cells associated with the neurovascular unit, including astrocytes, pericytes, myocytes and endothelial cells. They propose that apoE induces cerebrovascular dysfunction through direct signalling and indirectly via modulation of peripheral and central pathways. They also suggest that apoE predisposes the cerebral vasculature to damage by vascular risk factors and this results in modifications of blood flow, neuronal coupling and blood–brain barrier integrity. Thus, apoE4 may target multiple components of the vasculature to produce the overall effect on cognitive function.

Finally, Kalaria [3] reviews how different vascular pathologies cause brain tissue damage and attempts to identify key pathological substrates that cause vascular dementia with implications for Alzheimer's disease. In keeping with the focus on the interface between cerebrovascular and neurodegenerative pathologies in the other articles in the cluster, Kalaria emphasises that cerebrovascular changes [2] are frequent in late onset Alzheimer's disease. Although this has been known for more than 20 years there is now even more compelling evidence that vascular brain injury and pathology are components of Alzheimer's disease even in highly selected cohorts such as those in the National Alzheimer's Consortium Centre [10]. In addition, diffuse white matter changes with loss of myelin and axonal abnormalities are common to almost all subtypes of vascular dementia but also prominent in Alzheimer's disease. Medial temporal lobe and hippocampal atrophy accompanied by variable hippocampal sclerosis are widely accepted as consistent pathological features in Alzheimer's disease [7] but they are also apparent in vascular dementia. Investigating relevant genetic forms or suitable animal models with carefully defined approaches would be valuable in exploring the pathogenesis as well as identifying prevention strategies in the vascular causes of cognitive impairment irrespective of whether the outcome is vascular dementia or Alzheimer's disease.

Together, the articles in the present cluster provide a deep and novel interdisciplinary outlook on various aspects of vascular anatomy and pathology, brain imaging and clinical features for better understanding the molecular and cellular mechanisms associated with cerebrovascular pathology and dysfunction. Vascular disease risk factors are increasing worldwide and are likely to contribute to the burden of cognitive dysfunction and dementia. These articles provide not only further evidence for discussion of important substrates for cognitive impairment but there is now overwhelming support for the key role played by vascular factors in Alzheimer's disease.

## References


1. Carare RO, Hawkes CA, Jeffrey M, Kalaria RN, Weller RO (2013) Review: cerebral amyloid angiopathy, prion angiopathy, CADASIL and the spectrum of protein elimination failure angiopathies (PEFA) in neurodegenerative disease with a focus on therapy. Neuropathol Appl Neurobiol 39:593–611. doi:10.1111/nan.12042
2. Grinberg LT, Thal DR (2010) Vascular pathology in the aged human brain. Acta Neuropathol 119:277–290. doi:10.1007/s00401-010-0652-7
3. Kalaria R (2016) Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. Acta Neuropathol. doi:10.1007/s00401-016-1571-z **(in press)**
4. Love S, Miners S (2016) Cerebrovascular disease in ageing and Alzheimer's disease. Acta Neuropathol. doi:10.1007/s00401-015-1522-0 **(in press)**
5. Merlini M, Wanner D, Nitsch RM (2016) Tau pathology-dependent remodelling of cerebral arteries precedes Alzheimer's disease-related microvascular cerebral amyloid angiopathy. Acta Neuropathol. doi: 10.1007/s00401-016-1560-2 **(in press)**
6. Montagne A, Nation DA, Pa J, Toga AW, Zlokovic BV (2016) Brain imaging of neurovascular dysfunction in Alzheimer's disease. Acta Neuropathol **(in press)**

7. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS et al (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 123:1–11. doi:10.1007/s00401-011-0910-3
8. Morris AJW, Sharp MM, Albargothy NJ, Fernandes R, Hawkes CA, Verma A, Weller RO, Carare RO (2016) Vascular basement membranes as pathways for the passage of fluid into and out of the brain. Acta Neuropathol. doi:10.1007/s00401-016-1555-z **(in press)**
9. Tai LM, Thomas R, M. MF, Koster KP, Kanekiyo T, Morris AJW, Bu G (2016) The role of APOE in cerebrovascular dysfunction. Acta Neuropathol. doi:10.1007/s00401-016-1547-z **(in press)**
10. Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, Monsell SE, Kukull WA, Trojanowski JQ (2013) Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain 136:2697–2706. doi:10.1093/brain/awt188