

Stroke and dementia

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The burden of stroke and dementia

Dementia and stroke are two of the largest contributors to the global burden of disease. In Australia, the prevalence of dementia is projected to increase more than four-fold in the next four decades, from 245,400 people in 2009 to 1.13 million people by 2050 [1]. An estimated 1300 new cases of dementia are diagnosed each week in Australia. Worldwide, current dementia prevalence of 35 million is predicted to double every 20 years: an expected 66 million in 2030, 115 million in 2050 [2]. In Australia, 1 in 6 people will suffer a stroke in their lifetime, with global average of 15 million people stroke victims, killing 5 million and disabling another 5 million [3].

The association between stroke and dementia

Stroke is known to be a strong risk factor for the development of AD: a history of stroke doubles the risk of incident dementia in the older population [4]. In a recent meta-analysis [5], the authors found that after study methods and case mix were taken into account, reported estimates of the prevalence of dementia were consistent: 10% of patients had dementia before first stroke, 10% developed new dementia in the first few months after first stroke and 35% had dementia after recurrent stroke. At 5 years post-stroke, 30-50% of patients are demented [4, 5]. The strong association of post-stroke dementia with multiple strokes highlights the central causal role of stroke itself, as does the prognostic value of other stroke characteristics. There is no doubt that vascular risk factors are associated with dementia: data from several studies suggest that exposure to vascular risk factors in midlife increases the risk of dementia [6-8]. Whether these risk factors also affect structural brain aging and cognitive performance in non-demented individuals, however, remains unclear.

So how does stroke cause dementia? Every stroke is different, affecting different parts of the brain and hence different cognitive functions. Isolated cognitive deficits following stroke (e.g., aphasia, neglect) do not of themselves constitute dementia; rather they fall under the umbrella of vascular cognitive impairment. While both vascular dementia (VaD) and AD can occur alone, they are often associated. Pure vascular dementia is usually defined as due to cerebrovascular disease without other pathologies (using the AD staging system: “neuritic Braak stages 1.2-1.6”). Its prevalence in autopsy series is very variable, ranging from less than one percent to almost 60% (mean 8-15% in Western series, 22-35% in Japan) [9].

The great majority of patients in post-mortem studies have mixed pathologies: evidence of AD plus some vascular changes. In a 2009 population-based Cambridge over-75s cohort, 80% of demented patients had vascular pathology, and around 70% had AD pathology, with the majority of them mixed [10]. Individuals with both pathologies also appear to be more cognitively impaired than those with only one of the two. In the Nun Study (a famous longitudinal study following a group of women over decades), the authors found that AD patients with strokes had poorer cognitive function than those without [11-13].

Incident stroke worsens cognition in AD brains

In patients with established AD, the superimposition of stroke is associated with greater cognitive decline and worse prognosis. While it is known that there is significant overlap between risk factors for stroke and dementia, the contributions of arterial disease and cerebral hypoperfusion are not fully understood. In the Baltimore Longitudinal Study of Aging, the authors found that the presence of intracranial but not coronary or aortic atherosclerosis significantly increased the odds of dementia, independent of cerebral infarction [14]. Many of the risk factors for AD and stroke are the same, with the co-existence of risk factors – e.g., diabetes plus APOE ε4 homozygosity – being particularly additive.

Investigators from the Leukoaraiosis and Disability (LADIS) study found that incident lacunar infarcts on MRI are associated with a steeper rate of decline in executive functions and psychomotor speed, and when associated with white matter lesions (WML: chronic white matter ischaemic change or leukoaraiosis), lacunes determine longitudinal cognitive impairment [15]. In addition, they reported that the combination of atrophy in the medial temporal lobes and WML increased the risk of global cognitive impairment [16].

Stroke and amyloid: a potential association?

One potential mechanism for the association between stroke and dementia is amyloid. There are many theories for the pathogenesis of amyloid deposition, but a vascular theory suggests that a combination of cerebral hypoperfusion, together with the culmination of vascular pathology and senescence, leads to a neuroglial energy crisis, neuronal damage, cognitive damage and ultimately AD [17]. There is also evidence that the ischaemic cascade of stroke triggers amyloid deposition. Our understanding of the incidence on in-vivo amyloid has been enhanced with the advent of amyloid PET imaging. A breakthrough by Klunk and colleagues [18, 19] has enabled the imaging of amyloid plaques in neuronal tissue through the use of PiB and PET scanning, and studies investigating amyloid and cognitive changes following stroke are underway [20, 21]. PiB-PET enables antemortem imaging and quantification of amyloid deposition in the human brain [18, 19]. It is a carbon-11-labeled derivative of the thioflavin-T amyloid dye with excellent β -amyloid binding affinity and specificity [18, 19]. Antemortem PiB PET patterns of retention correlate well with amyloid deposition on post-mortem studies [22]. Early findings from our group suggest that there is a slightly increased number of stroke patients with positive amyloid imaging when compared to healthy community controls, but these data require confirmation [23].

Apolipoprotein E (ApoE) is a glycoprotein responsible for lipid transport in the brain and other organs. It exists in three isoforms ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) encoded by three alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) on chromosome 19 [24]. It confers considerable difference in terms of function and associated risk of disease. The $\epsilon 4$ allele was found to be a significant genetic risk factor in the development of sporadic AD [25]. A single $\epsilon 4$ allele increases the risk of AD approximately 3 times while two alleles confer up to 12 times the risk compared to non-carriers. It also increases the risk of vascular disease. As a result of impaired cholesterol transport and metabolism, both APOE $\epsilon 2$ and APOE $\epsilon 4$ accelerate atherogenesis. There is now evidence that APOE genotype is related to progression of chronic ischaemic white matter lesion load, as well as being associated with increased hippocampal atrophy [26, 27]

Vascular risk factors

In the North American Atherosclerosis Risk in Communities (ARIC) MRI study involving 1130 participants, Knopman et al. reported that vascular risk factors diabetes, hypertension, a history of stroke, and APOE $\epsilon 4$ genotype all independently contributed to cognitive decline in late middle age and early elderly years [28]. In a further study, the ARIC investigators found that both increased brain atrophy and evidence of stroke or ischaemic changes were driven by altered blood sugar and blood pressure control beginning in midlife [29].

Conclusion

With the aging of the baby-boomer generation, dementia has been identified as the greatest potential burden on health systems in most high-income nations [30]. A large proportion of these patients will have associated or superadded Alzheimer's pathology. These patients are therefore at high-risk cohort requiring urgent intervention to prevent increasing dependence and disability. It is important that we develop techniques to identify who will dement. We envisage a time when patients presenting with their first-ever stroke will be stratified into low- and high-risk categories, and their subsequent treatment will reflect this.

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TRACK RECORD FOR AMY BRODTMANN
(modified for 5 years FTE, see Career Disruptions pdf)

Introduction:

After completing post-doctoral training in cognitive neurology in Chicago, in 2006 I returned to Australia as a NHMRC ART Fellow to resume my research in stroke. I have continued my interest in dementia by establishing a focal onset dementia clinic – the first of its kind in Victoria – and developing new research projects in which the association between cerebrovascular disease and dementia is examined.

Qualifications:

- 2001-2004 PhD University of Melbourne 2004, Parkville, Melbourne, AUSTRALIA
1999 Admitted as a Fellow of the Royal Australian College of Physicians
1987-1992 MBBS (Medical Degree) University of Melbourne 1992, Parkville, Melbourne
- Positions:**
- 2009- present** Co-Director of Behavioural Neuroscience Group, Florey Neuroscience Institutes, Parkville and Heidelberg
2009-2010 National Brain School Co-ordinator, Australian and New Zealand Association of Neurologists, RACP
2005 – present Consultant Neurologist and Clinic Director, Eastern Cognitive Disorders Clinic, Box Hill Hospital, Box Hill, Melbourne, Australia
2007 – present Consultant Neurologist, AUSTIN HEALTH, Melbourne, Australia
2006 – Sept 2010 Australian Training Research Fellow, National Stroke Research Institute, Austin Health, Melbourne, AUSTRALIA
2004 - Research Associate, Cognitive Neurology and Alzheimer's Disease Center,
2005 Northwestern University School of Medicine, Chicago, Illinois, USA

Relevant Recent Publications:

1. Darby, D., **Brodtmann, A.**, Woodward, M., Budge, M., Maruff, P. Using cognitive decline in novel trial designs for primary prevention and early disease modifying therapy trials of Alzheimer's Disease *Int J Psychogeriatrics* in press 2011
2. **Brodtmann, A.** Cumming, T. Dementia and stroke: the present and future epidemic *Int J Stroke*. 2010 Dec;5(6):453-4.
3. **Brodtmann, A.** Puce, A, Darby, D, Donnan, G Regional fMRI brain activation does correlate with global brain volume *Brain Research* 2009 Mar 9;1259:17-25
4. **Brodtmann, A.** Puce, A, Darby, D, Donnan, G Post-stroke serial functional imaging reveals visual cortex reorganization *Neurorehab Neural Repair* 2009 Feb 23(2):150-159
5. **Brodtmann, A.** Puce, A, Darby, D, Donnan, G fMRI demonstrates diaschisis in extrastriate visual cortex *Stroke* 2007 Aug;38(8):2360-3
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7. Bradshaw, J, Saling, M, Hopwood, M, Anderson, V, **Brodtmann, A**, Fluctuating cognition (FC) in dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) is qualitatively distinct *JNNP* March 2004;75(3):382-7

Reviews and chapters:

1. **Brodtmann, A.** Cumming, T. *Dementia and stroke: the present and future epidemic* *Int J Stroke*. 2010 Dec;5(6):453-4
2. **Brodtmann, A.** *Dementia and diabetes* Diabetes Management September 2007 20:4-5
3. Brodtmann, A., Darby, D., Carey, L. Functional magnetic resonance imaging in stroke, *Magnetic Resonance Imaging in Stroke* edited by Stephen Davis, Marc Fisher and Steven Warach (Cambridge University Press, Cambridge, 2003)

Recent Presentations:

2010: *The Plastic Brain* Global Coaching Meeting, Sydney; 2010 Co-Chair, *Education in Neurology Symposium*, Australian and New Zealand Association of Neurologists Annual Scientific Meeting; 2009 *Does regional perfusion determine cortical remodelling? Functional and perfusion studies* Florey Neuroscience Institutes Symposium; 2009 *The Diagnosis and Management of Younger Onset Dementias* College of Clinical Neuropsychology Symposium; 2008 *Diaschisis in ventral visual cortex revealed by fMRI* Organization for Human Brain Mapping Stroke Satellite Meeting; 2008 *Brain recovery and rehabilitation after stroke* National Brain School, RACP

Awards:

- 2006** Australian Association of Neurologists Annual Scientific Meeting Young Investigator Awards Finalist
2005 Organization for Human Brain Mapping Travel Award
2003 Organization for Human Brain Mapping Travel Award
2003 Melbourne Abroad Travelling Scholarship
2002 Organization for Human Brain Mapping Travel Award
2001 RIKEN Neurosciences Institute Summer School Scholarship, Tokyo, Japan

Research Grants:

- 2011** Ross Trust grant
2011 Telematics Trust grant
2011 Brain Foundation Award
2011 JO & JR Wicking Foundation grant
2006-2010 **NHMRC Post-doctorate Australian Training Research Fellowship (part-time)**
2002 Austin Research Council grant for PhD project
2002 Pfizer CVL grant for PhD project
2001-2004 **National Health & Medical Research Council Post-Graduate Scholarship**

Teaching:

Weekly outpatient and ward round teaching of medical students and neurology trainees (Monash University and University of Melbourne); yearly lectures to neurology trainees via Brain School program and Victorian Neurology trainee lecture series; National Brain School Co-ordinator 2009-2010 overseeing monthly neurology curriculum delivery for all neurology trainees in Australia and New Zealand; organiser of dementia series for Masters program teaching for neuropsychology students (Monash University); bi-monthly Melbourne peer updates.

Theses Supervised:

Previous: Ettie Ben-Shabat (2008) Central processing of proprioception: functional neuroimaging and psychophysical studies in healthy and stroke participants (Latrobe University, physiotherapy)
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Editorial Responsibilities.

Regular reviewer for *Stroke*, *Neurology*, *Journal of Clinical Neurology and International Journal of Stroke*; occasional reviewer for *Eye and Brain*, *Brain*.

Experience in Clinical Trials and Population Health:

Involved in over 20 acute and chronic stroke trials and PI for more than 10 Alzheimer drug studies. Established first ever Victorian neurologist-run focal onset dementia clinic and FTD support group.

Committee memberships and other positions:

Fellow of the Royal of Australian College of Physicians, Australian and New Zealand Association of Neurologists, American Stroke Association, International Society to Advance Alzheimer Research and Treatment, World Federation of Neurology Research Group on Aphasia and Cognitive Disorders