Alzheimer's Research Review™

Making Education Easy

Issue 1 - 2012

In this issue:

Welcome to the first issue of Alzheimer's Research Review.

One of the studies in this issue assesses a new intranasal insulin therapy for Alzheimer's disease, and we also look at two imaging studies; one directly comparing FDG-PET scans and arterial spin labelling MRI, and another addressing the MRI changes seen in patients treated with monoclonal antibodies against Aβ. Also reviewed is an economic evaluation from the UK, which provides a strong case for the financial investment of early assessment.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them in the next issue. We hope you find the selections for this issue interesting, and we look forward to receiving your comments and feedback.

Kind Regards,

Associate Professor Michael Woodward
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Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment

A Pilot Clinical Trial

Authors: Craft, S et al.

Summary: This randomised, double-blind trial examined the effects of two different doses of intranasal insulin, compared with placebo, on cognition, function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with amnestic mild cognitive impairment or Alzheimer disease (AD). Participants received placebo (n = 30), 20 IU of insulin (n = 36), or 40 IU of insulin (n = 38) for 4 months, administered with a nasal drug delivery device. Treatment with 20 IU of insulin improved delayed memory ($P < .05$), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability ($P < .01$).

Comment: We desperately need new therapies for AD and its prodromal phases. Whilst the amyloid hypothesis is under some stress, innovative approaches that do not directly target amyloid are a light on the horizon. Insulin may affect a number of neuronal functions and has also been shown to interact with amyloid processing. There is impaired insulin and insulin-like growth factor expression and signalling mechanisms in AD that could deprive neurones of energy and increase oxidative stress. Indeed AD has been labelled type 3 diabetes. Recently rosiglitazone was found ineffective in those with AD, and caused fluid accumulation in a sizable proportion.

This moderately sized study showed encouraging cognitive and functional benefits of intranasal insulin which correlated with biomarker evidence of a response. The small doses of insulin appeared to be safe. Larger Phase III studies are warranted. It is however of concern that Type II diabetes, with elevated insulin levels, is also a risk factor for AD.

Reference: Arch Neurol. 2012; 69(1): 29-38
http://archneur.ama-assn.org/cgi/content/abstract/69/1/29

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Independent commentary by Associate Professor Michael Woodward, MBBS, MD, FRACP, Austin Health, Heidelberg, Victoria.

Associate Professor Woodward is Head of Aged and Residential Care Services and the Head of Memory Clinic at Austin Health. He is a specialist in geriatric medicine with major interests in dementia, quality use of medications, hypnosedatives and insomnia, wound management and vaccination of older people. He is also extensively involved in research trials on Alzheimer's disease and related disorders. As past Chair of the Australasian Consortium for Clinical Cognitive Research (AC4R) he is very involved in trial organisation and in attracting trials of new dementia therapies to Australia and New Zealand.

Associate Professor Woodward is author of numerous research and review articles as well as several book chapters on dementia therapies.

He is Chair of the 'Geriatric Therapeutics' editorial board of the Journal of Pharmacy Research and Practice.

Proteomic changes in cerebrospinal fluid of presymptomatic and affected persons carrying familial Alzheimer disease mutations

Authors: Ringman, J

Summary: The aim of this study was to identify cerebrospinal fluid (CSF) protein changes in persons who will develop familial Alzheimer disease (FAD) due to PSEN1 and APP mutations, using unbiased proteomics. The authors compared proteomic profiles of CSF from individuals with FAD who were mutation carriers (MCs) and related noncarriers (NCs). Fifty-six proteins were identified, represented by multiple tryptic peptides showing significant differences between MCs and NCs (46 upregulated and 10 downregulated); 40 of these proteins differed when the analysis was restricted to asymptomatic individuals.

Comment: The 'omic' field is producing a host of potential biomarkers that can be used to better understand the pathogenesis of the dementias as well as improve diagnosis and assist in monitoring disease programs, including response to therapies. This study on individuals sure to develop AD has revealed a host of CSF protein changes, some also found in those with non-familial late onset AD, that emphasize the importance of inflammation and neurodegeneration in AD.

Targeting these processes directly has already been attempted with little or no success even in non-demented populations (e.g. the ADAPT trial of celecoxib and naproxen- ref Martin et al, Arch Neurol 2008; 65: 696-905) but new therapies (e.g. etanercept) used early in those at high risk of AD may be a more successful approach.

Reference: Arch Neurol. 2012; 69(1): 96-104
http://archneur.ama-assn.org/cgi/content/abstract/69/1/96

Evidence for ordering of Alzheimer disease biomarkers

Authors: Clifford JJR, et al.

Summary: The authors of this study attempted to empirically assess the concept that Alzheimer's disease (AD) biomarkers significantly depart from normality in a temporally ordered manner. A total of 401 elderly participants in the Alzheimer's Disease Neuroimaging Initiative who were cognitively normal, who had mild cognitive impairment, or who had AD dementia were enrolled. Within each clinical group of the entire sample the CSF Aβ42 level was abnormal more often than was the CSF total tau level or the hippocampal volume (adjusted for intracranial volume). Among the 298 participants with both baseline and 12-month data, the proportion of participants with an abnormal Aβ42 level did not change from baseline to 12 months in any group. The proportion of participants with an abnormal total tau level increased from baseline to 12 months in cognitively normal participants (P = .05) but not in participants with mild cognitive impairment or AD dementia.

Comment: The (USA/Canadian) ADNI study is producing a vast array of data about the diagnosis, progression and other clinical features of cognitive decline and AD. This biomarker study is a little difficult to understand. Essentially, some AD processes begin and plateau before others and are reflected differently in the progressions of biomarkers. CSF Aβ42, reflecting the early pathogenesis of AD, changes before CSF tau and hippocampal volume with these latter two biomarkers reflecting neurodegeneration secondary to this pathogenesis. The lack of change over time in CSF Aβ42 suggests this biomarker has already plateaued in these individuals who have symptomatic AD and early AD (ie MCI). In those with a CSF Aβ42 suggesting amyloid accumulation, hippocampal volume seems to begin to decline before changes in CSF total tau, suggesting a sequence of change even in these markers of neurodegeneration. So, faced with an individual with cognitive impairment, biomarkers need to be assessed against clinical disease stage, and changes over time may add additional information. Waiting for an already abnormal (low) CSF Aβ42 to become more abnormal in an individual with an amnestic disorder will be futile, but progressive hippocampal atrophy in this individual could be diagnostic.

Reference: Arch Neurol. 2011; 68(12):1526-35
http://archneur.ama-assn.org/cgi/content/abstract/68/12/1526

The balance between cognitive reserve and brain imaging biomarkers of cerebrovascular and Alzheimer's diseases

Authors: Murray, AD et al.

Summary: This study examined the balance between brain magnetic resonance imaging (MRI) measures of the two most common pathologies associated with brain ageing, cerebrovascular disease and Alzheimer's disease, and parameters of cerebral reserve in well-characterized participants born in 1936, for whom childhood intelligence was known. Brain MRI was carried out at 1.5T using fluid attenuation inversion recovery and T1-weighted volumetric sequences in 249 participants. Educational attainment had a measurable and positive effect, with a standardized regression weight of +0.23, on late life cognitive ability in people without cognitive impairment aged 68 years. The authors demonstrated that the magnitude of the contribution of education is greater than the negative impact of either neuropathological burden alone, with standardized regression weights of –0.14 for white matter hyperintensities and –0.20 for hippocampal atrophy.

Comment: We are increasingly conceptualising AD as a balance between the accumulation of AD and other pathologies and the protection conferred by cerebral reserve. The latter is the result of life-long education which is layered onto childhood intelligence. Physical fitness, occupation and social interactions may also build up reserve, as well as reducing deleterious pathology. This study quantifies the burden of AD pathology using MRI measures of atrophy and cardiovascular pathology using white matter hyperintensities. Protection against this combined burden was indeed conferred by educational attainment but not occupation. So – choose your school well, study hard but then take whatever job comes. Oh, and keep socially engaged!

Reference: Brain 2011; 134(12): 3687-96
http://brain.oxfordjournals.org/content/134/12/3687.abstract

An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom

Authors: Getsios, D et al.

Summary: The authors of this study developed a discrete event simulation of AD progression and the effect of treatment interventions from data from donepezil trials and a 7-year follow-up registry amongst other sources. Simulated individuals were followed up for 10 years. In the base-case estimates, 17 patients needed to be assessed to diagnose one patient with AD, resulting in an average assessment cost of £4100 per patient diagnosed (2007 cost year). In comparison with a scenario without early assessment or pharmacologic treatment, early assessment reduced health care costs by £3600 per patient, and societal costs by £7750. Savings were also substantial compared with treatment without early assessment, averaging £2100 in health care costs, and £5700 in societal costs.

Comment: The theme of Alzheimer's Awareness week here in Australia this year, and of a major study by Alzheimer's Disease International was the benefits of early diagnosis. Using large data sets this UK study showed that not only is early diagnosis clinically sensible, it is also associated with cost savings. Some, but not all of these savings are related to earlier use of cholinerergic therapies. It makes good sense to achieve early diagnosis of a fatal disease for which we have effective if not curative therapies - the oncologists have known this for decades. These cost savings are likely to be even greater when we have truly disease modifying therapies.

Reference: Alzheimers Dement. 2012; 8(1): 22-30
http://tinyurl.com/6v4z2ra

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Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer's disease

Authors: Musieka, ES et al.

Summary: The utility of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in Alzheimer's disease (AD) diagnosis has been well established. Recently, measurement of cerebral blood flow using arterial spin labelling magnetic resonance imaging (ASL-MRI) has shown diagnostic potential in AD, and the authors of this study attempted to directly compare it with FDG-PET. Concurrent FDG-PET and ASL-MRI images were obtained in 17 AD patients and 19 age-matched control subjects. Both modalities revealed similar regional abnormalities in AD, as well as comparable sensitivity and specificity for the detection of AD after visual review by two expert readers. Interobserver agreement was better for FDG-PET (κ: 0.75) than ASL-MRI (κ: 0.51); intermodality agreement was moderate to strong (κ: 0.45–0.61); and readers were more confident of FDG-PET reads. Simple quantitative analysis of global cerebral fluorodeoxyglucose uptake (FDG-PET) or whole-brain cerebral blood flow (ASL-MRI) showed excellent diagnostic accuracy for both modalities, with area under receiver operating characteristic curves of 0.90 for FDG-PET and 0.91 for ASL-MRI.

Comment: FDG-PET is increasingly being used to "rule in" a diagnosis of AD, and indeed other dementias (e.g. DLB & FTLD), when used with clinical assessment. Unfortunately, access and cost are limiting factors in the utility of PET scanning. SPECT, a "poor man's PET", is much less accurate. MRI can be used to measure hippocampal atrophy but this is downstream from the hypometabolism FDG-PET can reveal, and not as specific for a dementia type as is the pattern of hypometabolism on FDG-PET. This study shows that arterial spin labelling on MRI may be an alternative to FDG-PET, and generally MRI is more accessible than PET. More work is needed but maybe speak now to your local MRI radiologist about developing skills in this technique.

Reference: Alzheimers Dement. 2012; 8(1): 51-59
http://tinyurl.com/cv3shye

Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI

Authors: Vos, S et al.

Summary: This study aimed to identify the best diagnostic test sequence for predicting Alzheimer's disease (AD)-type dementia in subjects with mild cognitive impairment (MCI) using cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) biomarkers. Of 153 subjects selected, 48 (31%) subjects had converted to AD-type dementia at follow-up in 2 years. In multivariable analyses, CSF beta amyloid (Aβ)1–42/tau ratio and hippocampal volumes (HCVs) predicted AD-type dementia regardless of apolipoprotein E (APOE) genotype and cognitive scores. Test sequence analyses showed that CSF Aβ1–42/tau increased predictive accuracy in subjects with normal HCV ($p<0.001$) and abnormal HCV ($p=0.025$). HCV increased predictive accuracy only in subjects with normal CSF Aβ1–42/tau ($p=0.014$).

Comment: The identification of prodromal AD, or MCI due to AD, is essential to informing prognosis and selecting individuals who may most benefit from therapies directed at AD pathology. This study shows that in those with clinically defined MCI, MRI - demonstrated hippocampal atrophy and CSF Aβ42/tau ratio are useful biomarkers to predict progressions to AD over 2 years. The CSF biomarkers performed somewhat better but the combination with MRI is likely to be more clinically useful.

It is however likely that PET amyloid imaging using new fluorinated ligands will become more widely used and can add additional information as demonstration of cerebral amyloid pathology in those with MCI (and in healthy non-cognitively impaired) seems to be a strong predictor of risk of future AD. Generally, this is more acceptable to individuals than CSF studies.

Reference: Neurobiol Ageing, available online 20 Jan 2012
http://tinyurl.com/7x47tzy

Cognition, glucose metabolism and amyloid burden in Alzheimer's disease

Authors: Fursta, AJ et al.

Summary: The authors of this study investigated relationships between glucose metabolism, amyloid load, and measures of cognitive and functional impairment in Alzheimer's disease (AD). Patients meeting criteria for probable AD underwent ^{11}C-labelled Pittsburgh Compound-B (^{11}C-PIB) and 18F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) imaging and were assessed on a set of clinical measures. The PIB distribution volume ratios and FDG scans were spatially normalized and average PIB counts from regions-of-interest were used to compute a measure of global PIB uptake. Separate voxel-wise regressions explored local and global relationships between metabolism, amyloid burden, and clinical measures. Regressions reflected cognitive domains assessed by individual measures, with visuospatial tests associated with more posterior metabolism, and language tests associated with metabolism in the left hemisphere.

Comment: Amyloid accumulation probably begins 10-15 or even more years before clinical symptoms in AD, whereas the effects of this amyloid, which include hypometabolism as measured by FDG PET, occur later. Thus, it is no surprise that this paper reveals a good correlation between the patterns of hypometabolism on FDG PET and clinical features (eg visuospatial features with posterior hypometabolism, language changes with left hemisphere hypometabolism). No such correlation was found between clinical features and amyloid load, as measured by PIB-PET, probably because amyloid accumulation was already maximal and widespread by the time these clinical features appeared.

In a similar vein, this reviewer is currently demonstrating a correlation between the degree of frontal hypometabolism on FDG-PET and a higher degree of clinical frontal/ behavioural features in AD (defining a frontal clinical variant of AD-"FvAD") – watch this space.

Reference: Neurobiol Aging 2012; 33(2): 215-25
http://tinyurl.com/8xxmook

Gantenerumab: a novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β

Authors: Bohrmann, B et al.

Summary: The amyloid-β lowering capacity of anti-Aβ antibodies has been demonstrated in transgenic models of Alzheimer's disease (AD) and in AD patients. While the mechanism of immunotherapeutic amyloid-β removal is controversial, antibody-mediated sequestration of peripheral Aβ versus microglial phagocytic activity and disassembly of cerebral amyloid (or a combination thereof) has been proposed. For successful Aβ immunotherapy, the authors of this study hypothesized that high affinity antibody binding to amyloid-β plaques and recruitment of brain effector cells is required for most efficient amyloid clearance. This article reports the generation of a novel fully human anti-Aβ antibody, gantenerumab, optimized in vitro for binding with sub-nanomolar affinity to a conformational epitope expressed on amyloid-β fibrils using HuCAL® phage display technologies.

Comment: A host of monoclonal antibodies against Aβ have been subjected to animal and human trials. These potentially disease-modifying agents offer a real hope for AD treatment. They act against differing regions of the 42 amino acids of Aβ and thus may have differing side effects and clinical responses.

Gantenerumab seems to act against aggregated Aβ oligomers, the most toxic form of Aβ, and may thus be the "holy grail" we have been looking for. This pathology study in animals shows the preference of this antibody for aggregated Aβ and an enhancement of cell – mediated Aβ clearance, but we have repeatedly seen in the AD therapies field that what works in test tubes and in animals may not work in humans. Roche are however currently testing this product in a large RCT of those with prodromal AD, positive for a CSF biomarker for AD.

Reference: J Alzheimers Disease 2012; 28(1): 49-69
http://tinyurl.com/7tb8wqh

Memantine and functional communication in Alzheimer's disease: results of a 12-week, international, randomized clinical trial

Authors: Saxton, J et al.

Summary: In this international, randomized, double-blind, placebo-controlled trial of memantine (10 mg bid), the functional communication abilities of patients with Alzheimer's disease (AD) (MMSE range: 10–19) were assessed using the Functional Linguistic Communication Inventory (FLCI). Two combined subscales (Social Communication and Communication of Basic Needs) from the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA FACS; secondary measure) were administered to caregivers. After 12 weeks, memantine-treated patients (n=133) demonstrated a non-significant improvement on the FLCI (placebo: −0.6; memantine: 0.7; p=0.070) and a significant improvement on the ASHA FACS (placebo: −5.3; memantine: 0.5; p = 0.022), compared with placebo-treated patients (n = 124).

Comment: The benefits of memantine on cognition, function and behaviour are well established. Communication – related benefits are less well studied and this 12 week RCT (with this reviewer as a co-author) showed a significant improvement on one measure of communication (the ASHA FACS) but not on another (the primary outcome, the FL CI). Larger studies are warranted but probably won't occur as generic memantine products are now available. My own patients' carers frequently report that memantine improves speech, engagement in group conversations and general social interactions of the person with dementia and it is good to find some data from an RCT to support this

Reference: J Alzheimers Disease 2012; 28(1): 109-18
http://tinyurl.com/7mc5cbt

Active cognitive lifestyle associates with cognitive recovery and a reduced risk of cognitive decline

Authors: Marioni, RE et al.

Summary: This study tested the association between cognitive lifestyle score and cognitive change in a population-based cohort of older persons from five sites across England and Wales. Data came from 13,004 participants of the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS) who were aged 65 years and over and were assessed at multiple waves over 16 years using the Mini-Mental State Examination. Cognitive lifestyle score was assessed as a composite measure of education, mid-life occupation, and current social engagement. Hazard ratios for cognitive lifestyle score showed significant differences between those in the upper compared to the lower tertile with a more active cognitive lifestyle associating with: a decreased risk of moving from no to slight impairment (0.58); recovery from a slightly impaired state back to a non-impaired state (2.93); but an increased mortality risk from a severely impaired state (1.28).

Comment: The protective effects of education, occupation and social engagement on cognition are well known. This data from the MRC-CFAS using over 13,000 participants has shown that not only is the combination of such activities apparently protective against moving from no to slight cognitive impairment as measured by the MMSE, but is also associated with a greater chance of moving from slightly to unimpaired. This data further supports the protective effects of "cognitive reserve" against accumulating dementia related pathology, but needs biomarker and neuropathology data to further tease out causality. Meanwhile – keep educated and engaged and be fortunate in your mid life occupation.

Reference: J Alzheimers Disease 2012; 28(1): 223-30
http://tinyurl.com/7n6y53l

Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis

Authors: Sperling, R et al.

Summary: In this study two neuroradiologists independently reviewed 2572 fluid-attenuated inversion recovery (FLAIR) MRI scans from 262 participants in two phase 2 studies of bapineuzumab and an open-label extension study. Two hundred and ten patients were included in the risk analyses. 36 patients (17%) developed vasogenic oedema and sulcal effusions (ARIA-E) during treatment with bapineuzumab; 15 of these ARIA-E cases (42%) had not been detected previously. 28 of these patients (78%) did not report associated symptoms. Adverse events, reported in eight symptomatic patients, included headache, confusion, and neuropsychiatric and gastrointestinal symptoms. MRI signal abnormalities suggestive of and microhaemorrhages and haemosiderin deposits (ARIA-H) occurred in 17 of the patients with ARIA-E (47%), compared with seven of 177 (4%) patients without ARIA-E. 13 of the 15 patients in whom ARIA were detected in our study received additional treatment infusions while ARIA-E were present, without any associated symptoms.

Comment: The monoclonal antibodies (mAbs) against Aβ, at least those directed at the N-terminus, seem to cause micro-haemorrhages and cerebral vasogenic oedema. These changes are now described as "ARIA": amyloid-related imaging abnormalities. Bapineuzumab is one such mAb and this analysis shows a 17% prevalence of ARIA with oedema and an 11.4% prevalence of ARIA with microhaemorrhages. The good news is that these appear to be largely radiological findings, with no symptoms, and indeed micro-haemorrhages are being found increasingly in AD patients with no mAb exposure. However, after our experience with active immunization (around 15% develop sterile meringoencephalitis, frequently symptomatic and sometimes fatal), we need to be cautious. If these mAbs prove effective, their use is likely to be excluded in those with a high baseline or subsequent burden of ARIA, and serial MRIs may be required to monitor safety.

Reference: Lancet Neurol. 2012; 11(3):241-9
http://tinyurl.com/6qe587w

