Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of neurodegenerative disease management

Fiona Kumfor^{*1}, Oliver Piguet¹ & Karen E Morrison²

Peters ME, Schwartz S, Han D et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. *Am. J. Psychiatry* doi: 10.1176/appi.ajp.2014.14040480 (2015) (Epub ahead of print).

Factors that predict progression in dementia are currently poorly understood. Here, Peters *et al* report the relationship between neuropsychiatric symptoms and progression to severe Alzheimer's dementia and death, using data from the Cache County Study. This population-based study began in 1995 and invited all Utah residents >65 years to participate. Over 5000 participants were recruited and assessed every 3–5 years. In this study, the 335 individuals diagnosed with possible or probable Alzheimer's disease were investigated and of these, 68 developed severe Alzheimer's disease during the study (1995–2010). Severe Alzheimer's dementia was defined as a Mini-Mental State Examination ≤10 or a Clinical Dementia Rating Scale score of 3 (severe). Presence of neuropsychiatric symptoms was determined using the informant-based Neuropsychiatric Inventory.

Notably, >50% of participants had at least 1 neuropsychiatric symptom, with 25% having at least 1 clinically significant neuropsychiatric symptom at baseline. Multivariate Cox regression analyses (controlling for age at onset, disease duration, gender, education, general health and APOE-4 status) revealed that psychosis, agitation/aggression and clinically significant neuropsychiatric symptoms were predictive of progression to severe dementia and death. Presence of affective symptoms (e.g., depression) and mild

neuropsychiatric symptoms were associated with earlier death only. These findings highlight the impact of neuropsychiatric symptoms on disease progression in Alzheimer's disease. Studies examining if treatment of neuropsychiatric symptoms modulates this relationship, warrant investigation. The nature and severity of neuropsychiatric symptoms in dementia varies, with these features occurring early in frontotemporal dementia. Whether a similar relationship is also observed in these non-Alzheimer's syndromes is yet to be determined.

– Written by Fiona Kumfor

Balconi M, Cotelli M, Brambilla M et al. Understanding emotions in frontotemporal dementia: the explicit and implicit emotional cue mismatch. *J. Alzheimer Dis.* doi: 10.3233/JAD-142826. (2015) (Epub ahead of print).

Disturbance of emotion processing is commonly observed in dementia. Such deficits are an early feature of frontotemporal dementia (FTD), more so in the behavioral than in the language variant of FTD. In Alzheimer's disease, changes in emotion processing tend to occur later in the disease process. In this study published in *J. Alzheimer's Dis.*, Balconi and colleagues explore the mechanisms underlying deficits in emotion recognition in 16 patients with the behavioral-variant of FTD, 12 with the agrammatic variant of primary progressive aphasia (the nonfluent language presentation of FTD), 14 with Alzheimer's disease, and 20 healthy controls, using explicit evaluation of emotions combined with measures of autonomic responses (skin conductance, heart rate) to these stimuli.

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Their investigations demonstrated that the FTD patients were just as good as patients with Alzheimer's disease and controls at distinguishing between images containing positive and negative emotions and between images with high and low arousal. In contrast, implicit responses to these stimuli were markedly reduced in the two FTD groups compared with the other groups. Reduction of the implicit responses was related to an increase in behavioral disturbance and with atrophy of the left putamen in these patients. These results demonstrate that although FTD patients understand broad emotional categories, they have difficulty experiencing or feeling these emotions. This discrepancy was particularly pronounced in the behavioral variant FTD group. These findings have implication for the management of FTD patients and their difficulty in relating to others in emotional situations.

– Written by Olivier Piguet

Lu C-H, Macdonald-Wallis C, Gray E *et al.* Neurofilament light chain A prognostic biomarker in amyotrophic lateral sclerosis. *Neurology* doi: 0.1212/WNL.0000000000001642 (2015) (Epub ahead of print).

Amyotrophic lateral sclerosis (ALS) is diagnosed clinically, progresses at a variable rate and, at present, there is no generally agreed biomarker that sensitively tracks disease progression or allows prediction of disease course. CSF and blood levels of neurofilament light chain (NfL) have been previously reported as markers of ALS disease activity. This study by Lu *et al.* adds to the data supporting serum levels of NfL as a biomarker for ALS with prognostic value.

In the study, a standard electrochemiluminescence measure of NfL was used in two cohorts of ALS patients and controls, assessing levels in serum, plasma and CSF at intervals up to 3 years. Patients were grouped according to the rate of change in ALSFRS-R score into slow, intermediate and fast progressing groups. The key results were that CSF NfL levels highly correlated with serum levels, these levels were overall about four-times higher in patients than controls and maintained at a fairly constant expression over time and, importantly, blood NfL levels determined at recruitment into the study were strong predictors of survival, and independent of other predictors such as rate of progression and age at symptom onset.

Confirmation of these results in other cohorts is eagerly awaited, particularly in rapidly progressing patients as there were few of these in the current study. It will also be important to look at blood and CSF NfL levels in earlier symptomatic ALS patients, and indeed in those in the presymptomatic stage, accessible through study of asymptomatic mutation carriers in families with known familial ALS mutations. Meanwhile, this study already adds sufficient evidence to suggest that blood NfL measurements should from now on be considered in stratifying patients in ALS therapeutic clinical trials.

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Fournier CN, Gearing M, Upadhyayula SR *et al.* Head injury does not alter disease progression or neuropathologic outcomes in ALS. *Neurology* 84, 1788–1795 (2015).

While many recent studies on ALS pathogenesis focus on genetic aspects there is also ongoing investigation into the role of environmental factors. Although several recent studies have failed to show an excess of head trauma prior to ALS diagnosis, the possibility that head injury may increase the rate of progression or influence the neuropathological features of ALS remains.

Fournier *et al.* address this in the above paper, in which they study the influence of head injury (defined as head injury associated with loss of consciousness or requiring hospitalization, occurring more than a year prior to ALS diagnosis) in their ALS clinic population. They report no difference in the rate of progression of the disease nor any difference in clinical features, including diagnosis of frontotemporal dementia, between those with and without a history of head injury. They also report no specific or distinct neuropathological features in ALS autopsy cases with antecedent head injury.

Although the study involved fairly small numbers of patients, and did not address the issues of milder or repeated head injury, the finding that antecedent head injury does not increase the rate of disease progression in patients seen in a typical ALS clinic is reassuring.

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