JOURNAL WATCH

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

Expert panel: Niklas Mattsson, Institute of Neuroscience & Physiology, the Sahlgrenska Academy at the University of Gothenburg, Sweden; Anne Rosser, Cardiff University Brain Repair Group, UK, and Neuroscience & Mental Health Research Institute, Cardiff University, UK; Duncan McLauchlan, Department of Psychological Medicine and Neurology, School of Medicine, University Hospital of Wales, UK; Theresa A Zesiewicz, University of South Florida, FL, USA

Kokjohn TA, Maarouf CL, Roher AE. Is Alzheimer's disease amyloidosis the result of a repair mechanism gone astray? *Alzheimers Dement.* 8, 574–583 (2012).

It is known that a large proportion of patients with sporadic Alzheimer's disease (AD) also have vascular brain pathology that may contribute to cognitive impairment. This is especially frequent in elderly patients, in whom studies suggest that 'pure AD' is exceedingly rare [1]. Few regard it as a pure coincidence that the incidence of AD mirrors the prevalence of hypertension, diabetes and stroke across the life-span, but precisely how these different pathologies interact is a matter of debate. In this position paper, Kokjohn and colleagues propose that there may be a direct causative link between age-dependent cardiovascular deficiency and β -amyloid ($A\beta$) brain deposition, which is a hallmark of AD. Their theory is that $A\beta$ deposition may be a physiological appropriate response to vessel injury, serving to uphold vessel integrity in acute stress. When chronically activated due to continuous wear and tear of the vascular system, this mechanism may go astray and become damaging to itself. The authors envision a vicious cycle, where $A\beta$ aggregation due to vascular damage in its turn may cause regional hypoxia and occlusion

of small vessels by increasing pressure on the vessels from external $A\beta$ deposits. The authors draw upon pathological evidence of associations between $A\beta$ plaques and occluded vessels, and biochemical evidence that $A\beta$ and amyloid precursor protein have properties linked to the coagulation system. It is an interesting argument that possibly may merge the amyloid cascade hypothesis with the empirical evidence of vascular pathology in AD patients.

– Written by Niklas Mattsson

Reference

- 1 Foruhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. *Nat. Rev. Neurol.* 5, 649–658 (2009).

Reiman EM, Quiroz YT, Fleisher AS *et al.* Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case–control study. *Lancet Neurol.* 11, 1048–1056 (2012).

The early bird catches the worm. That sums up the philosophy behind the ongoing studies of cognitively healthy carriers of mutations that are known to cause autosomal dominant Alzheimer's disease. In theory,

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such studies may reveal the pathological sequence of events leading to disease and clinical symptoms, and may also be instrumental in defining appropriate diagnostic and prognostic biomarkers at different disease stages. In a recent publication from the Dominantly Inherited Alzheimer Network (DIAN), Bateman *et al.* found a decline in the cerebrospinal fluid (CSF) levels of β -amyloid₄₂ (A β ₄₂) approximately 25 years prior to the expected symptom onset, followed by an elevation of CSF tau and brain deposition of A β ₄₂ [1]. These findings have now been complemented by a report from the Colombian Alzheimer's Prevention Initiative (API), where Reiman *et al.* describe preclinical biomarker changes in a cohort of presenilin 1 mutation carriers. Key findings are that these mutation carriers aged 18–26 years (approximately two decades prior to symptom onset) present functional MRI changes, reduced gray matter volume and increased levels of A β _{1–42} in CSF and plasma (but not increased levels of tau). Notably, this is prior to PET findings of brain A β deposition. The authors point to several important questions, such as whether the brain changes in mutation carriers are developmental or neurodegenerative, whether available PET techniques underestimate early A β plaque deposition and whether the CSF A β ₄₂ levels – although increased compared with noncarriers – had already started to decline in the mutation carriers in this study. In addition, the study was small; it was limited to 44 participants. However, the study protocols were harmonized with DIAN protocols, opening for future systematic comparisons.

– Written by Niklas Mattsson

Reference

- 1 Bateman RJ, Xiong C, Benzinger TL *et al.* Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N. Engl. J. Med.* 367(9), 795–804 (2012).

Richard IH, McDermott MP, Kurlan R *et al.*; SAD-PD Study Group.
A randomized, double-blind, placebo-controlled trial of

antidepressants in Parkinson disease. *Neurology* 78(16), 1229–1236 (2012).

Parkinson's disease has conventionally been thought of as a neurodegenerative disease marked by motor symptoms, including tremor, bradykinesia and rigidity. However, the importance of 'non-motor' symptoms, including mood, sleep disorders and dysautonomia, in Parkinson's disease has gained traction in the past 15 years. A closer look at the original monograph by James Parkinson in the early 1800s reveals that the scientist after whom this disease was named realized that the treatment of constipation, a non-motor symptom, greatly contributed to improvement in patients' quality of life.

In the present study (SAD-PD), Richard *et al.* report the findings of a randomized, double-blind, placebo-controlled trial of a selective serotonin reuptake inhibitor (paroxetine), and a serotonin and norepinephrine reuptake inhibitor (venlafaxine extended release) in the treatment of depression in Parkinson's disease. The 12-week study enrolled 115 patients from 20 movement disorder centers. Study participants met DSM-IV criteria for either a depressive disorder or had operationally defined subsyndromal depression. The primary outcome measure was the change from baseline to week 12 in the Hamilton-D (HAM-D) depression scale. Paroxetine and venlafaxine SR both significantly improved depression, and proved to be generally safe and well tolerated. The mean response in efficacy did not differ between the two antidepressants, and neither drug worsened motor function. The mean dosage of paroxetine at week 12 was 24 ± 11 mg/day, and the mean dosage of venlafaxine XR was 121 ± 75 mg/day. Although both drugs were generally well tolerated, one participant in the paroxetine group developed ventricular ectopy and withdrew from the study. This is the largest controlled study to evaluate the effect of commonly used antidepressants in Parkinson's disease, and provides evidence that paroxetine and venlafaxine XR are effective in treating depression in Parkinson's disease patients. Hopefully, it will not be the last.

– Written by Theresa A Zesiewicz

Labuschagne I, Jones R, Callaghan J *et al.*; The TRACK-HD Investigators.
Emotional face recognition deficits and medication effects in pre-manifest through stage-II Huntington's disease. *Psychiatry Res.* doi:10.1016/j.psychres.2012.09.022 (2012) (Epub ahead of print).

Emotion recognition deficits have been recognised in Huntington's disease (HD) for some time, and are thought to be an important element of the behavioural disturbance in this condition. There has been significant debate over whether these deficits are related to negative emotions, disgust in particular or emotion in general. The featured paper was part of the wider TRACK-HD study, a prospective, longitudinal study looking at a range of putative clinical, wet and imaging-based biomarkers in premanifest and manifest HD. Several questions are addressed, namely which emotions are affected, is there progression with disease status and, finally, is emotion recognition affected by a concurrent psychoactive drug prescription?

Three hundred and forty four participants aged 18–65 years with no prior neurological or psychiatric history were recruited across four sites. They were subdivided into two groups: 115 premanifest individuals, and 113 individuals with early HD. Controls were gene-negative family members or spouses. The most common medications were neuroleptics, most commonly atypical drugs for a variety of reasons (chorea, irritability, psychosis and depression) and selective serotonin re-uptake inhibitors (SSRIs; mostly for depression). Subjects were presented standardized faces from the Ekman and Friesen series for six emotions (happiness, sadness, anger, fear, surprise and disgust) and a neutral face. The stimuli were presented for 4000 ms, and the subjects were allowed 8000 ms to give a descriptive selection from the seven possible conditions. There were 70 trials in total (ten per facial stimulus).

In the pre-HD group, significant deficits were present in recognition of fear, anger and surprise with directionally equivalent, nonsignificant results for happiness,

sadness and disgust. Neutral face recognition was unimpaired. In the early HD group, impairment was found across all emotions including neutral faces.

Patients on SSRIs were better at recognizing sadness and disgust than participants not on medication, but patients taking neuroleptics were significantly worse at recognizing fear, happiness and sadness.

This is the largest longitudinal study of facial recognition in HD and suggests a progression of impaired facial emotion recognition with disease progression. It is also the first study to find impairment of neutral facial expression in early HD, but has not corroborated earlier work concerning the pre-eminence of impaired disgust recognition in the pre-motor stages of the disease. Importantly, this is the first study to show an effect of psychoactive medication on face recognition in HD (suggested in previous studies of SSRIs in normal controls), with obvious direct implications for patient management, although proof of causality will require further studies.

– Written by Duncan McLauchlan & Anne Rosser

Reedeker W, van der Mast RC, Giltay EJ, Kooistra TA, Roos RA, van Duijn E. Psychiatric disorders in Huntington's disease: a 2-year follow-up study. *Psychosomatics* 53, 220–222 (2012).

The neuropsychiatric features of Huntington's disease (HD) are often reported as being the most disabling aspects of the condition. A number of studies have attempted to quantify the prevalence and progression, with some contradictory

findings. Most such studies have used cross-sectional surveys of patients adjudged by their motor symptoms to be at different stages of the disease. This paper addresses the questions surrounding the predictors, incidence and prevalence of psychiatric disorders longitudinally according to DSM-IV criteria.

This single-center study originally recruited 142 genetically confirmed HD patients from a combination of outpatient clinics and a specialist HD nursing home. They were classified as presymptomatic (55 patients) or symptomatic on the basis of the Unified Huntington's Disease Rating Scale (UHDRS) and received the composite international diagnostic interview to assess for psychiatric disorders. In addition, the patients received cognitive assessments (Mini-Mental Score Evaluation [MMSE], stroop, verbal fluency and symbol digit modalities test) and background demographics were recorded. Thirty six patients were lost to follow-up for various reasons (psychopathology was similar at baseline to the rest of the group, but MMSE scores and functional capacity were lower). Of the remaining subjects, 14 developed a new psychiatric disorder, which was depression in the majority of cases; seven had a persistent disorder (although the diagnosis changed in most); and eight had a disorder that remitted (depression, social phobia and obsessive–compulsive disorder). The predictors of a disorder included the use of psychotropic medication, childlessness, previous psychiatric diagnosis, less education and lower total functional capacity.

This study is the first longitudinal assessment of formally diagnosed psychiatric disorders in HD according to DSM-IV criteria (as opposed to dimensional assessments of

symptomatology) and is consistent with current thinking about the behavioral symptoms in HD, namely that they show variable prevalence rather than the steady progression associated with motor and cognitive symptoms. The use of formal psychiatric diagnoses in a neurodegenerative disease can be difficult as some aspects of the diagnostic criteria may reflect the disease itself rather than a feature of a new psychiatric condition. By contrast, many patients display features of psychiatric disorders, but do not meet formal diagnostic criteria. The exclusion of those with dementia and the higher dropout rate may underestimate psychopathology. This study adds to the work of Thompson *et al.* who used a dimensional instrument to assess psychopathology [1].

– Written by Duncan McLauchlan & Anne Rosser

Reference

- 1 Thompson JC, Harris J, Sollom AC *et al.* Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J. Neuropsychiatry Clin. Neurosci.* 24(1), 53–60 (2012).

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Journal Watch highlights some of the most important papers recently published in the field of neurodegenerative disease management and research. The editorial team welcomes recommendations for relevant papers for inclusion in future issues.

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