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 and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden; Amy Evans, Cardiff University Brain Repair Group, Cardiff, UK; Anne Rosser, Cardiff University Brain Repair Group, and Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK; Victoria Robertson, Cardiff University Brain Repair Group, Cardiff, UK; Alysia Battersby, Cardiff University, Cardiff, UK; Susan Fox, Movement Disorder Clinic, Toronto Western Hospital, and Division of Neurology, University of Toronto, ON, Canada; Philippe Huot, Movement Disorder Clinic, Toronto Western Hospital, and Division of Neurology, University of Toronto, ON, Canada

Dubois B, Tolosa E, Katzenschlager R et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. *Mov. Disord.* doi:10.1002/mds.25098 (2012) (Epub ahead of print).

Parkinson's disease (PD) is usually regarded as a motor disease. However, with disease progression, cognitive symptoms arise and, after 15–20 years of disease evolution, dementia can affect up to 80% of PD patients. Cholinergic denervation is believed to play an important role in dementia in PD. Thus, the basal forebrain cholinergic system undergoes degeneration, and brain acetylcholine levels are lower in PD patients with dementia (PDD) than in PD patients without dementia. To date, the cholinesterase inhibitor rivastigmine has shown efficacy in PDD [1]. Donepezil (5–10 mg daily) has been previously assessed in a small cross-over randomized controlled trial involving 22 subjects with a nonsignificant improvement in the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) compared with placebo trials and no significant adverse events [2]. The current study was the first large, multinational, randomized, double-blind, placebo-controlled

study to assess the safety and efficacy of donepezil in PDD patients. Patients with moderately advanced idiopathic PD, aged 40 years old, with cognitive decline meeting the DSM-IV criteria for dementia and a Mini-Mental State Examination (MMSE) score between 10 and 26 were included. Subjects with dementia with Lewy bodies (i.e., dementia within 1 year of motor symptoms) were excluded. A total of 550 patients from 108 sites were randomized, 195 in the donepezil 5 mg daily group, 182 in the donepezil 10 mg daily group and 173 in the placebo group, for 24 weeks of treatment. One study co-primary efficacy end point was the change from baseline to week 24 in ADAS-Cog; the other co-primary efficacy end point was the change from baseline to week 24 in Clinician's Interview Based Impression of Change with caregiver/study partner input (CIBIC+) subscale. Several secondary efficacy measures were also assessed: Brief Test of Attention; Delis-Kaplan Executive Function System™; verbal fluency battery; MMSE; Disability Assessment for Dementia scale; Unified Parkinson's Disease Rating Scale; Schwab and England scales; and Neuropsychiatry Inventory. Statistical analysis was performed on an intent-to-treat basis, and last observation carried forward was used

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to account for missing values. At week 24, the ADAS-Cog score improved in the donepezil treatment groups (both 5 and 10 mg), although this failed to reach statistical significance when compared with placebo. At week 24, donepezil 10 mg daily, but not 5 mg daily, significantly improved the CIBIC+ score, when compared with the placebo group. At week 24, the MMSE, Delis-Kaplan Executive Function System and Brief Test of Attention scores were all significantly improved by donepezil, 5 and 10 mg daily, when compared with placebo. Scores of the Disability Assessment for Dementia scale, Schwab and England and Neuropsychiatry Inventory tests were not significantly altered by donepezil, 5 or 10 mg daily, when compared with placebo. Cholinergic adverse events were most commonly reported, but occurred in all three arms of the study, although were more frequent in the donepezil arms. There were no significant changes in the Unified Parkinson's Disease Rating Scale, although tremor was reported as an adverse event in the donepezil groups (7.2 compared with 2.9% placebo). Although donepezil therapy failed to achieve one of its co-primary end points, an improvement of the ADAS-Cog score at week 24 when compared with placebo, it nevertheless met its other co-primary end point, it improved the CIBIC+ score and resulted in a significant improvement in a battery of cognitive tests. As such, donepezil represents a potential therapy for PDD patients, and the study suggests that donepezil 10 mg daily may be more efficacious than donepezil 5 mg daily. A recent Cochrane review of the use of cholinesterase inhibitor in PDD [3] also concluded that, overall, this class of drug is useful in PDD, without any benefit of donepezil compared with rivastigmine.

– Written by Philippe Huot & Susan Fox

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van Vliet R, Breedveld G, de Rijk-van Andel J *et al.* *PRRT2* phenotypes and penetrance of paroxysmal kinesigenic dyskinesia and infantile convulsions. *Neurology* 79, 777–784 (2012).

Paroxysmal kinesigenic dyskinesia (PKD)/choreoathetosis is a disorder characterized by brief attacks of dystonia, chorea, athetosis or ballism, which occur after a trigger, such as sudden movement. PKD can occur alone or in conjunction with benign (nonfebrile) familial infantile convulsions (BFIC), in which case it is termed infantile convulsion choreoathetosis (ICCA) syndrome. Previous studies [1–3] have identified mutations in *PRRT2*, located on chromosome 16p11.2, as an etiological factor in PKD, BFIC and ICCA; although the penetrance and phenotype caused by *PRRT2* mutations in these disorders remain unknown. In order to determine the genotypic/phenotypic correlation of *PRRT2* mutations in PKD, BFIC and ICCA, the authors performed clinical and genetic studies. This included sequencing the coding region of *PRRT2* in 61 subjects from three large families with ICCA, two smaller families with ICCA and four individuals with PKD without infantile convulsions. Many of the subjects screened also suffered from migraines. Clinical data were collected by using a structured questionnaire, and by performing a standard neurological examination. Data were also gathered regarding the clinical characteristics of PKD attacks, infantile convulsions and migraine attacks. When possible, medical records were reviewed. In the patients screened, neurologic examination was unremarkable and available EEG, brain computed tomography and MRI demonstrated no abnormalities. The male:female ratio was 1.6:1.0. Average age of onset of PKD attacks was 10.87 years and the attacks decreased during adolescence.

Most of the attacks were triggered by sudden movements and consisted of choreiform (70%), dystonic (52%) and athetotic (13%) movements; most of the attacks lasted less than 1 min. The frequency of the attacks was variable, but could be as high as 50 per day. Premonitory symptoms, such as uncontrolled feeling or tingling of the extremities, were experienced by 62% of patients. Up to 38% of the subjects said they could suppress the attacks by tightening the affected body part, slowing down the movement, sitting still or remaining in motion. Frequency and symptomatology of the attacks were not influenced by education level, smoking, coffee intake, alcohol consumption or circadian rhythm. Migraine was experienced by 31 of the enrolled subjects; of these, 16 had migraine with aura and three had hemiplegic migraine.

DNA genomics were isolated from venous blood. DNA sequencing was performed following PCR amplification of the DNA genomics. Three heterozygous mutations were detected in subjects with PKD. The first one had been previously reported, c.649dupC (p.Arg217Profs*8). The second one was a novel missense mutation, c.824C>T (p.Ser275Phe), whereas the third one was a novel truncating mutation, c.649C>T (p.Arg217*). No mutation could be identified in two patients with PKD. In addition, none of these mutations were detected in 662 chromosomes from control Caucasian subjects. The penetrance of *PRRT2* mutations was estimated to be 61% when the PKD phenotype was considered alone, whereas it reached 90% when PKD and infantile convulsions were both considered. Mutations in *PRRT2* were recently identified as an underlying cause of PKD, ICCA and BFIC. The data from the current study provide evidence that these three disorders are part of a single disease spectrum with a common genetic cause.

– Written by Philippe Huot & Susan Fox

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Lo RY, Jagust WJ; Alzheimer's Disease Neuroimaging Initiative. Vascular burden and Alzheimer disease pathologic progression. *Neurology* 79, 1349–1355 (2012).

Vascular pathology is exceedingly common in the elderly, and is a major cause of cognitive impairment and dementia. Vascular risk factors also influence the clinical progression of Alzheimer's disease (AD) dementia; however, it is still not clear if vascular disease mechanistically influences the development of AD pathology in the brain. The major brain hallmarks of AD are extracellular β -amyloid deposits and intracellular tangles composed of tau proteins. However, the correlations between these changes and clinical dementia decline with age, and elderly dementia patients often have mixed pathologies rather than pure AD pathology. One theory is that vascular disease accelerates brain β -amyloid accumulation; however, vascular disease and AD may also be two separate entities, increasing the likelihood of developing cognitive symptoms with increasing age, if they are both present simultaneously. Lo and Jagust set out to determine the relationship between vascular disease and AD by cross-examining biomarkers of different types of pathologies in the well-characterized Alzheimer's Disease Neuroimaging Initiative cohort of controls, mild cognitive impairment patients and AD dementia patients. They used cardiovascular risk scores and MRI white matter hyperintensities as surrogate markers for vascular burden, and used longitudinal changes in PET, MRI and cerebrospinal fluid measurements of AD pathology as outcome measurements. Interestingly, the overriding result was that the vascular pathology surrogates did not influence progression of the AD

biomarkers. This suggests that the vascular contribution is additive to the AD pathology, rather than exerting its effects by accelerating the development of major AD hallmarks. However, it should be noted that the Alzheimer's Disease Neuroimaging Initiative cohort was selected specifically to exclude major vascular disease, and that the follow-up may have been too short to detect milder effects.

– Written by Niklas Mattsson

Pouladi MA, Brillaud E, Xie Y *et al.* NP03, a novel low-dose lithium formulation, is neuroprotective in the *YAC128* mouse model of Huntington disease. *Neurobiol. Dis.* 48, 282–289 (2012).

Lithium is an alkali metal that has been used to treat bipolar disease for many years. More recently, it has been reported to have neuroprotective effects in animal models of Alzheimer's disease and Huntington's disease (HD). However, a constant practical problem with lithium treatment has been its narrow therapeutic window, with low doses having little impact and higher doses increasing the toxicological effects. Here, the authors explored an alternative method of drug delivery, NP03, in which lithium is delivered in a water and oil microemulsion, which passes relatively easily through the blood–brain barrier. This allows satisfactory lithium brain levels at markedly lower blood levels, thus lowering the risk of side effects. This treatment was trialed in the *YAC128* mouse model of HD, in which striatal atrophy and neurodegeneration result in progressive cognitive dysfunction and motor deficits, from 2–3 months of age. Daily treatment of *YAC128* mice with NP03 from 2–12 months of age produced significant reductions in motor deficits from 8 months with no adverse effects and reduced striatal atrophy compared with vehicle-treated animals.

The authors attempted to determine the mechanisms underlying these encouraging results and demonstrated a number of changes consistent with some correction of the underlying pathogenic features of HD. Levels of mutant huntingtin were

reduced in NP03-treated animals, and the elevated caspase-6 activity usually found in *YAC128* mice striatum was attenuated. Brain-derived neurotrophic factor levels, which are depressed in HD, increased following NP03 treatments. In addition, the proposed neuroprotective properties of lithium have previously been attributed to increased phosphorylated Akt levels or the inhibition of GSK-3 through phosphorylation. This study found no differences in striatal phospho-Akt levels between NP03- and vehicle-treated *YAC128* mice. However, an inhibition in GSK-3 levels was found in NP03-treated animals. The authors, therefore, propose a combined mechanism for the alleviation of HD-related symptoms in treated mice. Along with previous positive results in *YAC128* and N171–82Q HD mice, NP03 is proposed as a potential therapeutic agent for HD.

– Written by Amy Evans, Victoria Robertson & Anne Rosser

Tsunemi T, Ashe TD, Morrison BE *et al.* PGC-1 α rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. *Sci. Transl. Med.* 4(142), 142ra97 (2012).

Huntington's disease (HD) is caused by an expansion of the polyglutamine tract in HTT. Mutant HTT undergoes a conformational change, causing it to misfold, resist degradation and aggregate. Mutant HTT also interferes with the transcription of nuclear genes, including *Pgc-1 α* , a master regulator of transcription programs required for mitochondrial energy production and for countering reactive oxygen species. The disruption of PGC-1 α is believed to be a major cause of mitochondrial dysfunction in HD. This study found that restoring *Pgc-1 α* function in a mouse model of HD ameliorates HD neurological phenotypes and neurodegeneration. The authors also found that *Pgc-1 α* overexpression virtually eliminates all HTT aggregates, indicative of an improved protein turnover. Protein aggregation is enhanced in oxidative milieus, and the

authors showed that PGC-1 α -mediated mitigation of oxidative stress could indeed reduce HTT aggregation. However, given the dramatic reduction of HTT aggregation, the authors considered whether PGC-1 α might be more closely linked to protein turnover. They discovered that PGC-1 α switches on the activating transcription factor EB (TFEB), a master regulator of the autophagy–lysosome pathway, which is involved in eliminating misfolded proteins in the CNS. Furthermore, *Tfeb*

overexpression alone reduced mutant HTT aggregation and neurotoxicity, a quality that is likely to be of relevance to all polyglutamine disease proteins. This study yielded improved HD phenotypes, with both PGC-1 α and TFEB, making them attractive targets for drug testing for HD, as well as for further investigations in other diseases caused by protein misfolding.

– Written by Alysia Battersby
& Anne Rosser

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