

## New Insights into the Pathophysiology of SUDEP – Results from the MORTEMUS Study

**Reviewer: Dr Aidan Neligan, UCL Institute of Neurology, Queen Square, London, UK.**

Sudden unexplained death in epilepsy (SUDEP) is the most common epilepsy-related cause of non-accidental death in adults with refractory epilepsy. It is estimated that the incidence is approximately four deaths per 1000 patient-years which translates into a 12% cumulative risk over 40 years for people with uncontrolled childhood-onset epilepsy. It is well-recognised that the incidence of SUDEP is higher in more severe epilepsy and in people with generalised seizures. It is also more likely to occur at night with nocturnal supervision suggested to have a protective effect. Whilst SUDEP is believed to be a post-ictal event, with the few documented cases of witnessed SUDEP occurring in the aftermath of a generalised convulsive seizure, the exact pathophysiology and risk factors for SUDEP are poorly understood.

Philippe Ryvlin and colleagues carried out a retrospective survey of 147 epilepsy-monitoring units in Europe, Israel, New Zealand and Australia (the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS)) between 1st of January 2008 and the 29th December 2009. In total 29 cardiorespiratory arrests were reported, of which 16 cases were classified as eight definite (SUDEP for which post-mortem examination failed to reveal a cause) and eight possible (SUDEP for which post-mortem examination was not available, with no other suspected cause) SUDEP. There were nine cases of near SUDEP (whereby patients survived resuscitation for more than one hour after the cardiorespiratory arrest) and four cases of deaths from other causes.

The 29 events were reported by 27 different units from 11 countries, with all non-monitored SUDEP and fatal near SUDEP occurring at night in a unit where nocturnal staff numbers were at a level comparable to a standard neurological ward. In all but one case of monitored SUDEP, the event occurred between 19:30 and 06:00. Cardiorespiratory resuscitation (CPR) was performed in 11 of the 16 cases of SUDEP and all cases of fatal near SUDEP with an average delay greater than 10 minutes after the initial apnoeic episode. In contrast CPR was initiated within three minutes of all cases of near fatal SUDEP, six of which occurred during the daytime.

In all assessable cases a seizure occurred immediately before the cardiorespiratory arrest, which was a generalised tonic clonic seizure (GTCS) in all SUDEP cases and seven of the nine near SUDEP cases. Tapering or cessation of anti-epileptic drugs (AEDs) (in order to capture a seizure) occurred in nine cases of GTCS-induced cardiorespiratory arrest, none of whom had a GTCS in the preceding three

months. Respiratory distress was observed in almost all cases of SUDEP prior to terminal arrest underlining the compulsory need for the use of pulse oximetry alarm systems on all epilepsy monitoring units. The risk of definite or probable SUDEP per 10,000 video EEGs was 1.2 (0.6-2.1) in adults; 2.1 (1.0-3.8) in those undergoing pre-surgical evaluation compared to 0.2 (0.0-1.2) undergoing vEEG for other reasons.

Several conclusions can be inferred from this study: 1) The majority of cases of SUDEP occur at night mandating improved levels of nocturnal supervision on epilepsy monitoring units 2) All cases of observed SUDEP occurred in the aftermath of a convulsive seizure 3) Tapering or cessation of AEDs is a clear risk factor for SUDEP 4) Breathing difficulties are a prominent feature in the sequence of events preceding cardiorespiratory arrest in all cases of SUDEP. The routine use of pulse oximetry monitoring systems should be mandatory on all epilepsy monitoring units.

**Ryvlin P, Nashef L, Lhatoo SD et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol* 2013;12:966-77.**

## Long-Term Cognitive Impairment After Critical Illness

**Reviewer: Sian K Alexander, Addenbrooke's Hospital, Hills Road, Cambridge, UK.**

Cognitive impairment is often seen in patients following admission to critical care units, and anecdotally acknowledged to be common amongst physicians. However, studies of the incidence and causes of this cognitive impairment have been lacking, and where performed have been generally small in size and limited in scope. In this paper, Pandharipande et al describe a robust multi-centre study of 821 patients enrolled at the time of ICU admission. They assess pre-morbid cognition using a quantitated informant questionnaire, measure duration of delirium using research-trained observers and quantify doses of major classes of centrally-acting drugs (including benzodiazepines, propofol and other analgesic and sedative medications). Outcome measures of global cognitive performance (using the Repeatable Battery for the Assessment of Neuropsychological Status, RBANS), and executive function specifically, were assessed at three and twelve months. Patients with severe cognitive impairment were excluded from the study, and only 6% of the studied cohort had pre-existing cognitive impairment.

Twelve months after ICU admission, 34% of patients had cognitive impairment akin to that of moderate traumatic brain injury (TBI), with 24% of these patients having cognitive impairment two standard deviations below the mean, equivalent to mild Alzheimer's disease.

Observed length of delirium was directly correlated with long-term cognitive impair-

ment, which will be unsurprising to many. The relationship between delirium in the context of acute illness and long-term cognitive impairment remains an area of active investigation. It is unclear whether a set of risk factors predispose a patient to both, or whether the specific toxic insults in delirium, and associated response of neurohormones and cytokines, mediate neuronal pathophysiology with longer-term sequelae. A more surprising finding was that cognitive outcome was not related to exposure to sedative and analgesic medication, contrary to my intuitive hypothesis. Importantly, young patients (aged 49 years or younger) were not exempt from the risk of cognitive impairment; similar rates were seen in young and older patients alike.

This study provides important information on the frequency of cognitive impairment in the critical-care setting and does well to achieve follow-up in this cohort at twelve months. The relationship between critical illness and long-term cognitive impairment is an important subject for research, not least because it is one that acutely affects rehabilitation in patients and the perception of recovery for patients' families. This study provides important information on the frequency of cognitive impairment in the critical-care setting and does well to achieve follow-up in this cohort at twelve months. Nevertheless, further work to evaluate the profile of cognitive impairment over longer periods of time remains an important area to address: do patients experience progressive impairments akin to those with sporadic Alzheimer's disease? Or is this a static or even reversible phenomenon? This information is important to guide rehabilitation strategy and counselling of patients and families. Finally, although this study did not identify any protective strategies for the prevention of cognitive impairment, this would be an interesting avenue for further research.

**Pandharipande PP, Girard TD, Jackson JC et al (BRAIN-ICU Study Investigators). Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306-16.**

## Hands up if You're Better

**Reviewer: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust.**

The measurement and quantification of improvement is fundamental to the process of rehabilitation. Ensuring that specific interventions and approaches work as opposed to "seeming to" work is important in meeting patient's needs. Or is it?

This study looks at the changes in upper limb function that can follow a stroke and compares quantified improvements on standardised scales with patient perceptions of improvement.

Because upper limb function is complex

and multi-dimensional, there is no single scale that can adequately capture impairment and change. There is a difficulty, therefore, in knowing how well our attempts at measuring improvement or response to therapeutic interventions actually relate to an individuals own view of their impairments and consequent disabilities.

The "objective" scale used as a comparator, here, is the Action Research Arm test (ARAT), which evaluates common upper limb movements that form part of everyday functioning, but in an abstract setting. This was set against the "subjective" Motor Activity Log (MAL) and the Stroke Impairment Scale (SIS). These are both self-report scales that measure perceived ability in a variety of specific functional activities.

The exclusion criteria around upper limb baseline function, cognitive and communication impairments meant that of 200 potential participants only 39 were able to participate. This challenge of recruitment will be familiar to anyone who has attempted upper limb functional trials.

When comparing the objective and subjective measures of improvement, there was significant matching for outcomes between the ARAT and the MAL but not the SIS. This means that for the latter scale there is a mismatch in how well patients perceived they have progressed and how much things have actually changed.

Interestingly, the two main factors that predicted this mismatch were level of education and mood. A lower level of education and better mood scores were both predictive of a greater match between the objective and subjective scales. While intuitively, one would expect a lower mood to associate with poorer self-image and perception of progress, the connection between educational level and mismatch is a little harder to conceptualise. Perhaps this discrepancy may arise because of different expectations or even exposure to other (not always reliable) information around recovery from non-clinical sources. Either way it is, perhaps, important to consider self-reported and subjective measures of change as meaningful outcomes for the individual.

**Van Delden AL, Peper CL, Beek PJ et al. Match and Mismatch between Objective and Subjective Improvements in Upper Limb Function after Stroke. Disability and Rehabilitation. 2013;35:1961-67.**

## PD Psychosis: A New Drug on the Block

**Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.**

Psychosis, comprising of hallucinations and delusions, affects more than half of patients with Parkinson's disease, especially later in the course of the disease. It can be a major source of patient and caregiver stress, and frequently leads to hospital admissions, and earlier nursing home placement. Pharmacological

approaches to managing psychosis in Parkinson's disease can be disappointing, and sometimes come at the cost of deterioration in motor disability. Whilst quetiapine is frequently used in everyday practice, double blind placebo controlled trials have demonstrated safety but not efficacy. Similarly, data on the effectiveness of cholinesterase inhibitors is limited. The best evidence to date is for clozapine, an atypical antipsychotic which has a favourable side effect profile in terms of having minimal impact on motor function. However, it is infrequently prescribed as a first line treatment due to safety concerns and haematological monitoring requirements. Thus, there is a clear clinical gap for new therapeutic agents able to confer antipsychotic benefit in Parkinson's disease without harmful side effects.

A recent well-designed study published in the Lancet demonstrated that pimavanserin, a selective serotonin 5-HT<sub>2A</sub> inverse agonist, may be able to address this unmet need. In a six week, double-blind study, 199 patients with Parkinson's disease psychosis were randomly assigned to receive pimavanserin 40mgs once daily or matched placebo. Patients were assessed at baseline and days 15, 29 and 43 using the PD-adapted scale for positive symptoms (SAPS-PD), which is a nine-item scale rating symptoms like delusions and hallucinations. Pimavanserin treated patients had clinically significant improvements on this scale, and tolerated the medication well without experiencing sedation or worsening motor scores on the UPDRS. Treatment benefit was independent of age and cognitive status.

Outcomes were independently assessed by raters, investigators and carers enabling us to have much more confidence in the results. On the back of these study outcomes, licensing applications are now to start in Europe and the US, with plans to also trial this drug in Alzheimer's disease.

**Cummings J, Isaacson S, Mills R et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2013 Oct 31;S0140-6736.**

## Neurodegeneration: Paving a Pathway Through Protein

**Reviewer: Jemeen Sreedharan, Dept of Neurobiology/ Neurology, University of Massachusetts Medical School, Worcester, USA.**

Going into neurodegeneration research may be considered by some to be academic suicide. Indeed, we have failed to develop effective therapies for these progressive diseases, despite our growing knowledge of the genetic causes and improved clinical and pathological phenotyping. Thus, it was with incredible excitement that the work of the Malluci lab at the MRC Toxicology Unit in Leicester was widely publicised by the media, including BBC television (Moreno et al 2013).

Moreno et al used a transgenic mouse over-expressing mouse wild-type prion protein (PrP<sup>C</sup>). This mouse does not get ill. However, after inoculating the brain with PrP<sup>Sc</sup> extract (i.e. PrP with the pathological beta pleated conformation) the animal develops progressive behavioural changes and motor impairment culminating in death just 12 weeks after inoculation. Classical PrP<sup>Sc</sup> inclusions, spongiform cortical changes and neurodegeneration are seen, mimicking human spongiform encephalopathies such as CJD.

In work published in Nature in 2012 the Malluci lab showed that a critical pathway was active in these mice: the Unfolded Protein Response (UPR). The UPR is thought to be one mechanism by which a cell deals with accumulating misfolded proteins, which are a hallmark of neurodegenerative diseases. It is activated by a molecular sensor (BiP) in the endoplasmic reticulum followed by a phosphorylation cascade involving PERK and then eIF2 $\alpha$ . The outcome is a temporary shutdown of protein synthesis. In the PrP mice activation of the UPR resulted in a dramatic reduction in synaptic protein synthesis, synapse loss and neuronal death. Strikingly, genetically inhibiting the UPR pathway using lentiviral RNA interference prevented this catastrophic neural degeneration (Moreno et al 2012).

The breakthrough in the current paper from the same lab is that an orally bioavailable agent, a highly specific PERK inhibitor called GSK2606414, was used to globally inhibit the UPR throughout the mouse brain with dramatic effect. Mice treated before symptom onset never developed disease and there was no neurodegeneration, despite ongoing accumulation of misfolded PrP. Importantly for us as clinicians, animals treated after disease onset also responded with a stabilisation of their phenotype.

This result is astounding in its magnitude, suggesting that such a destructive process as spongiform encephalopathy could be treated with a pill. However, Malluci is mindful to point out that PERK inhibition does lead to unwanted effects in her PrP mice, including weight loss and glucose intolerance. Nonetheless, it has not escaped her attention that the UPR is activated in the brains of patients with ALS, Alzheimer's disease and Parkinson's disease and it is exciting to speculate that PERK inhibition may thus have therapeutic potential in the broader context of neurodegeneration. It may be that a careful balance between UPR activation and inhibition may be necessary to allow a neuron to deal with cellular stress without culminating in irreversible synaptic loss. Further compound screening, testing and trials are clearly urgently warranted.

**Moreno JA, Halliday M, Molloy C et al. Oral treatment targeting the unfolded protein response prevents neurodegeneration and clinical disease in prion-infected mice. Sci Transl Med. 2013 Oct 9;5(206):206ra138.**

**Moreno JA, Radford H, Peretti D et al. Sustained translational repression by eIF2 $\alpha$ -P mediates prion neurodegeneration. Nature. 2012 May 6;485:507-11.**