

29th International Epilepsy Congress

CONFERENCE REVIEW

Making Education Easy

28th August - 1st September 2011, Rome, Italy

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Welcome to our review of the 29th International Epilepsy Congress held in Rome

from 28th August - 1st September 2011. Dr Paul Timmings from Waikato attended the congress and considered the following abstracts and posters to be of particular interest. He gained particular insights from the sessions about epilepsy and mortality, as well as the video sessions about unusual seizures. These and other studies presented at the congress can be found at <http://onlinelibrary.wiley.com/doi/10.1111/epi.2011.52.issue-s6/issuetoc>.

At the congress Dr Timmings participated in the EpiNet symposium where Dr Peter Bergin spoke about the NZ-driven EpiNet project as a research tool. Dr Timmings also presented a paper at the European EEG photosensitivity consortium symposium (a satellite meeting).

We hope you find this review of the International Epilepsy Congress interesting and useful in your current practice.

Kind regards

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The evolution of visual field loss in individuals who continue vigabatrin therapy over a ten-year period

Authors: Clayton L et al

Summary: This study evaluated the long-term evolution of vigabatrin-associated visual field loss (VAVFL) in patients treated for 10 years. Fourteen vigabatrin recipients had their visual fields assessed by Goldmann perimetry over a 10-year treatment period (mean follow-up period 128 months). The prevalence of VAVFL increased from 64% at the first examination to 93% after 10 years. Visual field size decreased significantly over the treatment period but showed a high degree of variability between successive test sessions. All patients had a decrease in visual field size with increasing cumulative vigabatrin exposure. In conclusion, exposure to vigabatrin over a 10-year period results in progressive VAVFL that is hard to detect because of the high degree of variability in visual size field between test sessions.

Comment: Vigabatrin continues to represent a useful anti-epileptic drug (AED) for some patients. This study confirms our suspicions that the effect on visual field constriction progresses with continued vigabatrin therapy. The decreased visual field size is demonstrably linked to cumulative exposure and illustrates that complacency with respect to visual field monitoring is misplaced. It appears that the clinician would be wise to continuously ask whether the benefit of prescribing vigabatrin outweighs the risk, especially in the context of other new AEDs that are becoming available.

Abstract p068

Local drug delivery of levetiracetam in the rat model of acquired epilepsy using PLGA biodegradable polymer sheet implantations

Authors: Beattie N et al

Summary: This study examined the effect of biodegradable polymer PLGA loaded with 10% levetiracetam on seizures in a rat model of acquired epilepsy. Post-kainic acid status epilepticus rats received bilateral subdural implantation of PLGA sheets loaded with 10% levetiracetam or blank PLGA sheets. A third group were sham operated. Video EEG recordings were performed over a 6-week period. The mean number of seizures/24hr was 0.111 in rats implanted with PLGA + levetiracetam compared with 1.513 in non-implanted controls. In conclusion, levetiracetam implanted intracranially via polymer sheets has anticonvulsant effects in a rat model of acquired epilepsy.

Comment: This report from our Australian colleagues informs us of exciting delivery developments for AEDs. Biodegradable implantable polymers can allow direct delivery of therapeutic agents to the brain, thus allowing use of lower doses whilst mitigating adverse effects associated with systemic administration and bypassing the blood-brain barrier. This animal study demonstrates proof of concept, with evidence of efficacy and tolerability over a 6-week period. Although considerable development work is needed, this novel AED delivery strategy represents a promising approach and will be "a space to watch".

Abstract p518

SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

Sudden unexpected death in epilepsy (SUDEP) safety checklist: a way of quantifying and describing a patient's risk of SUDEP using a practical clinical checklist on a single sheet

Authors: Cox D et al

Summary: This study described the development of a clinical visual checklist of risk factors for SUDEP. A detailed review of current literature was undertaken, and the identified risk factors were divided into very low, low medium and high risk using the Australian risk mapping system for safety checklists (AS4360). The resulting visual checklist with a simple tick box design facilitates assessment of an individual's risk and the overall severity of risk on a given date. The checklist can be used to prioritise clinical activity based on mortality risk, and becomes a baseline against which future progress or deterioration can be measured. In conclusion, an easy reference checklist for SUDEP has been developed that can be quickly completed during a clinic visit.

Comment: This and several following papers were part of a half-day session about epilepsy and the associated increased risks of death. In many countries SUDEP remains poorly understood, incompletely reported and inadequately discussed with patients. Development of a 1-page checklist to help discuss SUDEP with patients represents progress because it encourages discussion about the risks and consideration of ways to reduce the chance of SUDEP. The risk factors remain unchanged i.e. age 20–40 years, GTCs, night seizures, imperfect seizure control, and poor compliance or sudden medication changes. Putting this all on one page and discussing risk and ways to reduce risk with the patient and family during a clinic visit will be helpful.

Abstract: p056

Postictal decerebrate rigidity: clinical evidence of the involvement of cerebral electrical shutdown combined with respiratory distress as a possible mechanism of SUDEP

Authors: Cenusu M et al

Summary: This case report discussed the occurrence of cerebral electrical shutdown combined with cerebral hypoxia/anoxia as a possible mechanism of SUDEP. A 17-year-old female patient with cryptogenic epilepsy underwent intensive EEG-video monitoring. A secondary generalised seizure was recorded during monitoring (left frontal origin). Typical flattening of the EEG was observed postictally. Severe respiratory distress with hypoventilation and apnoeic phases occurred during the immediate postictal phase, despite the patient being put into a semi-prone position. The EEG during this phase remained flat. After about a minute the patient presented with opisthotonic posturing typical for decerebrate rigidity, that stopped after respiration normalised. In conclusion, although not resulting in SUDEP, this case supports the hypothesis that postictal hypoventilation can lead to failure of recovery of cortical function and subsequent cardiac failure.

Comment: This case report is helpful in our understanding of mechanisms of SUDEP. Because very few SUDEPs have actually been recorded whilst patients have been monitored, our knowledge of mechanisms remains imperfect. This case report contributes useful additional clinical data, which although anecdotal, does also convey additional insight into mechanisms of postictal hypoventilation and the subsequent downward spiral of cardio-respiratory embarrassment.

Abstract: 007

Circadian seizure patterns in SUDEP: patients with nocturnal seizures are at highest risk

Authors: Lamberts R et al

Summary: This study evaluated circadian seizure patterns of SUDEP. Data from 154 autopsy-confirmed SUDEP cases and 616 living epilepsy controls were reviewed. Analysis of information on seizure patterns in the last 3 months revealed that people who died of SUDEP were more likely than controls to have a history of nocturnal seizures (odds ratio 3.9, 95% CI 2.5–6.0). In conclusion, nocturnal seizures are an independent risk factor for SUDEP.

Comment: This is a large multicentre UK and European study of SUDEP risk factors. It supports earlier observations that SUDEP is more likely to occur at night, particularly during sleep. Independent risk factor analysis demonstrated that SUPEP-in-sleep victims were 3.6x more likely to have a history of nocturnal seizures, and amongst all SUPEP the probability of a history of nocturnal seizures was 3.9x. This means that our patients with sleep-only seizures are at greater risk than we have previously perceived and that clinicians should strive to attain seizure freedom spanning the whole 24h period, not just during the day. The paper recommends improved night supervision, which although desirable, may be impractical.

Abstract: 009

Reduced heart rate variability is associated with ictal hypoxemia

Authors: Bateman L et al

Summary: This study evaluated factors contributing to SUDEP. Patients who underwent elective inpatient video-EEG telemetry monitoring for medically intractable partial epilepsy had their EEG and EKG recordings reviewed. From a total of 96 temporal onset seizures with accompanying oxygen saturation data, 32 seizures had no oxygen desaturations <90%, 32 had desaturations <90%, and 32 had progression to generalised convulsions. Mean seizure duration was 103 seconds. Mean heart rate variability (HRV) measured by SDNN was 51.9 in seizures with no desaturations <90%, 40.2 in seizures with desaturations <90% without secondary generalisation and 32.1 in seizures with secondary generalisation ($p=0.027$ vs seizures without desaturations <90%). In conclusion, HRV is reduced in seizures with greater oxygen desaturation (particularly in those with secondary generalisation) and may contribute to the pathophysiology of SUDEP.

Comment: Reduced HRV is linked to increased risk of death and SUDEP. Reduced HRV appears to be a marker of impaired autonomic regulation and this is linked to increased risk of death. The purpose of this study was to establish whether it is a primary or secondary phenomenon. In this Californian based video-EEG study, reduced HRV was linked to greater oxygen desaturation but this was only noted when secondarily generalised seizures occurred. It is therefore suggested that reduced HRV is a secondary phenomenon, related to the seizure severity, particularly secondary generalisation. This again emphasises to us that generalised seizures increase risk of SUDEP and suggests reduced autonomic regulatory function secondary to relative hypoxaemia as a contributory mechanism.

Abstract: 012

Effect of interictal epileptic activities on heart rate variability in unilateral temporal lobe epilepsy

Authors: Kinoshita M et al

Summary: This study investigated whether interictal epileptic activities affect HRV in patients with temporal lobe epilepsy of unilateral foci. Eight adult patients (mean age 39 years) with clinically defined unilateral temporal lobe epilepsy were monitored monthly ($n=2$) or yearly ($n=6$) during sleep by EEG and ECG. 20 events of interictal EEG epileptic activities (12 left-sided and 8 right-sided) were selected. HRV indices of high frequency component, low frequency component, and their ratio were analysed using 30-sec of ECG before and after events. The high-frequency component of HRV before and after right-sided events was significantly lower than that of left-sided events. High-frequency significantly increased after left-sided events. The low frequency:high frequency ratio after left-sided events was lower than that after right-sided events ($p<0.05$). In conclusion, cardiac parasympathetic tone may be suppressed in patients with epileptogenic foci in the right temporal lobe, but may increase after interictal epileptic activities in the left temporal lobe.

Comment: Continuing the SUDEP theme. HRV is useful as a marker of autonomic stability and reactivity. Reduced HRV may be associated with SUDEP. This study demonstrates reduction of parasympathetic tone in seizure of right temporal onset and an increase in parasympathetic tone if the seizure arose in the left temporal lobe. This might be relevant to reduced HRV associated with some seizures, and may be site of seizure onset specific. Thus potentially also representing a separate risk factor for SUDEP.

Abstract: 010

EPILEPSY-ASSOCIATED MORBIDITY AND MORTALITY

The frequency and associated risk factors of seizure-related injury, near-drowning and vehicular crashes in a community sample of patients with epilepsy

Authors: D'Souza W et al

Summary: This study investigated the frequency and risk factors for seizure-related injury, near drowning and vehicular crashes in a community sample of patients with epilepsy. 997 patients with epilepsy on the Tasmanian Epilepsy Register (TER) were assessed for lifetime and 12-month frequency of injury, near drowning and vehicular crashes by a validated interviewer-administered questionnaire. The estimated lifetime and 12-month frequencies were 20.4% and 6.3%, respectively, for any injury; 7.4% and 1.8%, respectively, for bathing or swimming injuries; and 7.5% and 0.5%, respectively, for vehicular crashes. The most common specific types of injuries were head injuries (8.6%) and burns/scalds (6.0%). Multivariate analysis revealed that younger age at epilepsy onset, poor seizure-control and a diagnosis of IGE were independent risk factors for seizure-related injury.

Comment: Continuing the theme that having epilepsy increases risk of accident and death, Wendyl D'Souza presented results of a community-based Tasmanian study in people with epilepsy. This is in contrast to most other mortality and injury studies which have been hospital- or specialty clinic-based. These results illustrate to us that epilepsy is not a benign condition, and needs to be taken seriously by patients, doctors and regulators. Of particular concern is the lifetime risk of motor-vehicle crash of 7.5%, and the annual crash risk of 0.5%. Again, poor seizure control features as a factor that we should be able to modify. And again we see that management of IGE is also more important than many of us have previously considered.

Abstract: 011

Cause-specific mortality among patients with epilepsy: results of a 40-year cohort study

Authors: Granbichler C et al

Summary: This study investigated the factors associated with higher-than-expected death rates in patients with epilepsy. All patients with confirmed epilepsy treated at an outpatient epilepsy clinic from 1970–2009 were enrolled and followed through December 2009. Standardised mortality ratio (SMR) was calculated using reference rates from the same region. 826 of 4752 patients died during follow-up. Age-adjusted overall SMR was 1.7 (95% CI 1.6–1.9). The highest SMRs were seen during the first year after diagnosis (2.3), and in patients who had used >4 AEDs in history (2.3), had recurrent seizures (2.2), had generalised epilepsies (2.0), or had a history of status epilepticus (2.0). The highest cause-specific SMRs were for epilepsy (68.3), brain tumours (14.6), congenital anomalies (6.5), and suicide (4.0). In conclusion, ongoing seizure activity, a high number of AEDs, generalised epilepsies and previous status epilepticus contribute to the higher-than-expected risk of death in patients with epilepsy.

Comment: This Austrian study reports almost 63,500 patient-years of follow-up, which represents a mammoth project spanning 40 years. The authors present sobering SMR data, which emphasises to us that epilepsy is not a benign condition, with an overall SMR of 1.7. Poor seizure control and increased death risk in the 1st year after diagnosis merit particular consideration. In addition a 4x greater risk of suicide (95% CI 1.8–7.5) is also of particular concern.

Abstract: 008

RISKS OF PRENATAL EXPOSURE TO AEDS

Valproate dose is an independent risk factor for autism spectrum disorder: evidence from prospective assessments in the Australian Brain, Cognition and Antiepileptic Drugs study

Authors: Wood A et al

Summary: This study investigated the association between autism spectrum disorder traits and *in utero* exposure to AEDs. 103 children aged 6–8 years whose mothers took AEDs during pregnancy were recruited via the Australian Pregnancy Register. Assessment of autism spectrum traits was performed using the Conners Autism Rating Scale (CARS). 11 out of 103 children (10.7%) exceeded the CARS threshold. Of these, 2/26 were exposed to valproate monotherapy (7.7%), 2/32 to carbamazepine monotherapy (6.3%) and 7/15 to polytherapy with valproate (46.7%). No child exposed to polytherapy without valproate exceeded the CARS threshold. First trimester valproate dose was significantly associated with CARS scores ($p < 0.05$). In conclusion, these data demonstrate a higher rate of autism traits after foetal AED exposure than previously reported, particularly with valproate polytherapy.

Comment: Concern about the impact of valproate (VPA) on the unborn child beyond standard teratogenicity issues continues to mount. This study of autism spectrum features in 103 children exposed to AEDs *in utero* is limited by very low numbers affected. However it does demonstrate a bias towards autism spectrum when VPA was taken as part of AED polytherapy. These data in combination with 3rd trimester data suggesting reduced final IQ in children exposed to VPA *in utero* should cause us to review VPA use during pregnancy and perhaps to even more strenuously avoid it.

Abstract: p079

Prenatal exposure to antiepileptic drugs: cognitive functioning at six years of age

Authors: Bromley R et al

Summary: This study investigated the effects of *in utero* exposure to AEDs on cognitive function. Women with epilepsy and healthy controls were recruited from antenatal clinics and their offspring were followed for 6 years. Sodium valproate exposure *in utero* ($n=51$) was associated with a significant decrease in scores for general cognitive ability, language comprehension, expressive language, memory, auditory attention and rate of learning (all $p < 0.001$). Children exposed to valproate had an increased incidence of educational needs and speech therapy (both $p < 0.001$). Prenatal exposure to carbamazepine ($n=50$) or lamotrigine ($n=30$) was not associated with poorer cognitive outcomes at age 6 years. In conclusion, children exposed to valproate *in utero* should be monitored closely during early childhood to allow for early intervention.

Comment: More evidence suggesting that VPA exposure *in utero* may impact on cognitive development. This UK study has generated concerns similar to the previously published Australian study, suggesting that cognitive development is impaired in children exposed to VPA *in utero*. Although similar numbers of CBZ- and LTG-exposed children were also evaluated, a similar impact on cognitive development was not noted. This again demonstrates that risks and benefits of VPA use in pregnancy should be carefully weighed.

Abstract: 024

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Independent commentary by Dr Paul Timmings
MB ChB FRACP. Otago graduate.

Dr Timmings is a Hamilton and Waikato DHB neurologist, with a particular interest in epilepsy. He is currently involved in research using change in EEG photosensitivity as a surrogate marker of anti-epileptic-drug efficacy.

COGNITIVE DECLINE IN EPILEPSY

White matter network abnormalities are associated with cognitive decline in chronic epilepsy

Authors: Vaessen M et al

Summary: This study investigated the association between white matter network abnormalities and cognitive decline in patients with chronic epilepsy. 39 patients with non-symptomatic localisation-related epilepsy and 23 age-matched healthy controls underwent diffusion MRI and neuropsychological (IQ) assessment. Whole brain white matter networks were constructed from fiber tractography, and weighted graph theoretical analysis was performed to determine the association between white matter connective abnormalities and cognitive decline. Patients with severe cognitive impairment showed lower clustering (a measure of brain network segregation) and higher path length (a measure of brain network integration) than healthy controls and patients with little or no cognitive impairment, but whole brain white matter volume was normal. IQ and the degree of cognitive impairment were strongly correlated with clustering and path lengths. In conclusion, patients with chronic epilepsy have impaired white matter connectivity that is associated with cognitive decline.

Comment: This Netherlands study links impaired white matter tract connectivity, reduced cognitive capacity and chronic localisation-related epilepsy. These researchers have established that disruption of white matter tract connections outside the epileptic zone are a contributor to cognitive impairment in patients with longstanding epilepsy. There was no difference in whole brain volume, and so they presume that the problem lies with network connectivity and topology

Abstract: p538

Loss of network efficiency associated with cognitive decline in chronic epilepsy

Authors: Vlooswijk M et al

Summary: This study investigated the association between possibly altered whole brain topology and intellectual decline in patients with chronic epilepsy. 41 adults with cryptogenic localisation-related epilepsy and 23 healthy controls underwent neurocognitive assessment, and fMRI with graph theoretical network analysis. Healthy controls were found to have efficient small world properties but patients with epilepsy had disruptions of local segregation and global integration. An association of more pronounced intellectual decline with more disturbed local segregation was observed in the patient group. In conclusion, chronic localisation-related epilepsy appears to cause cognitive deficits by inducing global cerebral network changes.

Comment: This study suggests that localisation-related epilepsies can be linked to diffuse cognitive decline due to disruption of global cerebral network efficiency and alteration of network topology. The topology changes are not limited to the epileptic zone and are more widespread. It is not clear whether this is as a consequence of whatever is causing the epilepsy, or the effect of recurrent seizures, or as a consequence of AED treatment. The concept is intriguing but more work is needed to tease it out further.

Abstract: p536

PatientsLikeMe® epilepsy community: an insight into symptoms and side effects reported online by patients with epilepsy

Authors: de la Loge C et al

Summary: This study described the symptoms and side effects reported by epilepsy patients on the free online PatientsLikeMe® platform that was launched in the USA in January 2010. By September 2010, 1838 users diagnosed with epilepsy had registered on the site and 1341 had completed the symptoms list. 74.4% of patients who completed the list had treatment data available: 54.7% were taking polytherapy, 52.9% were taking newer AEDs, 17.4% were taking older AEDs, and 29.7% were taking newer and older AEDs combined. 88.1% of patients reported ≥1 moderate/severe symptom, including memory problems (60.5%), concentration problems (53.4%), fatigue (49.5%), and somnolence (42.5%). In conclusion, cognitive problems, fatigue and somnolence were the most commonly reported moderate/severe symptoms in patients using the PatientsLikeMe® site.

Comment: A live on-line demonstration of the PatientsLikeMe® internet platform was presented. This internet site invites patients with various diseases to sign up to a secure web based network. They are invited to enter as much information as they feel comfortable sharing. They can enter diagnoses, treatments, seizure records, and all manner of symptoms and side effects. If they give permission, these data can be seen by other users. The program can be used to inform patients about possible research studies in their disease, and who to contact if they wish to be considered for participation. It also allows users to make queries about how many patients are taking what, or the incidence of various side effects etc. It could become a powerful social networking, emotional support, and research tool. It appears that the data entered are unfiltered, and so represent each patient's "view of the world", which may have limitations for any subsequent scientific analyses.

Abstract: p476

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References: 1. PHARMAC funding criteria.

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