

EDITOR'S CHOICE

The dangers of complex partial status epilepticus

This study identified 96 patients with their first status epilepticus episode by retrospective search of records. Fifteen patients died. Only five patients had non-convulsive status with coma but three of these died. For the purposes of this study 11 patients whose non-convulsive status was due to global anoxia were excluded but they all died as well. There were six deaths out of 42 patients with complex partial status and six out of 45 with convulsive status suggesting a similar mortality of 14%. All of the four patients with simple partial status survived. Of the 15 patients who died, 14 had what the authors call a potentially fatal aetiology, although the definition of this is not clear. Looking at it the other way around, of 56 with a potentially fatal aetiology, 75% survived. So, as in previous studies, the cause of the seizures was a key factor in predicting mortality, but even in the worst aetiological group there were many survivors. In this study additional variables were identified which carry a poor prognosis, including older age and severity of coma. Interestingly, duration of status over one hour was not an independent adverse predictor. Previous studies have suggested that Caucasians carry a higher risk but this was not borne out once the confounding influence of age was removed.

Probably the single most striking result of this study was the severity of the outcome for patients with complex partial status. What I could not glean from the data was whether this group were more likely to have a potentially fatal aetiology. Intuitively this is likely to be the case since most complex partial status is due to structural brain disease, whereas tonic clonic status may be due to treatable factors such as alcohol withdrawal, drug overdoses and metabolic derangements. This piece of information is important in deciding if patients with complex partial status need to be treated as aggressively as those with convulsive status.

-MRAM

Rosetti AO, Hurwitz S, Logroscino G, Bromfield E.

Prognosis of status epilepticus: role of aetiology, age and consciousness impairment at presentation.

JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2006;77:611-15.

ALZHEIMER'S: don't forget the olive oil

Sloshing around the epidemiological literature for some time has been the suggestion that the Mediterranean diet is good for you. Fish, olive oil and wine in good measure, a fair amount of dairy products and low meat intake, keep the doctor away. And also Alzheimer's, if this New York group are to be believed. 4166 individuals started in the Washington-Heights-Inwood Columbia Aging Project and this particular study focused on the prospective follow-up of the 3436 that were not demented at the outset. Unfortunately, useful information on diet could only be gleaned from 2258 subjects, of mean age 77 years, who were followed-up every 1.5 years. 11% (n=262) developed Alzheimer's during the mean four years of follow-up. However, those who stuck to the diet were 40% less likely to develop the disease than the less compliant; this finding stood a rigorous testing for confounds. Not given in the text is the number needed to treat, which my trusty calculator tells me is around eight. Happily for this reviewer, those components of the Mediterranean diet which seemed especially helpful were alcohol and vegetables! But the combo seemed to be the best of all. Of critical importance to any reader, ignored by the authors, is how long people need to have been on the Mediterranean diet to gain its protective effect? Can I stick with my "modified Atkin's diet" until 70 years old and then switch? Or do I need to stockpile the extra virgin olive oil now? -AJC

Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA.

Mediterranean diet and risk for Alzheimer's disease.

ANNALS OF NEUROLOGY

2006;59(6):912-21.

PRION DISEASE: learning from cannibalism

*** RECOMMENDED

There is something gothic about the history of the prion hypothesis: the triumph of one sole thinker against establishment (as Pruisner would have it) on the sinister backdrop of the threat of a pandemic of dementia. This research in the Lancet, amazingly simple at heart, follows the tradition. A six-man team with "heavy-vehicle rescue equipment" patrolled the Papua New

Guinea highlands for cases of kuru, the cerebellar prion disease transmitted by ritual cannibalism. Since this practice was outlawed in the mid 1950s, the incubation period could be defined by the most recent incident cases. Since 1996, eleven kuru patients have been found. The minimum incubation period for these people could be calculated at between 34 and 41 years. This is considerably greater than previous estimates of the mean incubation period of 12 years. Most of the affected patients were heterozygous for methionine and valine at position 129 in the PrP gene. The implication is that variant CJD, caused by eating prion-infected beef, may have a similarly extended incubation period. The authors remind us that the cow-to-man species barrier tends to prolong incubation periods. And one interpretation of the dominance of methionine homozygosity at PrP129 in the 160 cases of vCJD to date is that heterozygotes have a greater incubation period.... and so will make up a "second epidemic". Since rendering and butchering techniques were modified to reduce or abolish the risk of prion protein infectivity by 1990, new cases of vCJD may still be appearing in 2030 or so.... or not. We'll have to wait and see. -AJC

Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas D, Alpers M.
Kuru in the 21st century—an acquired human prion disease with very long incubation periods.

THE LANCET

2006;367:2068-74.

HUNTINGTON'S DISEASE (HD): supporting the striatum in HD with GDNF

GDNF has a long history with Parkinson's disease but in a recent issue of PNAS it has been shown to be useful in Huntington's disease. In this study GDNF was delivered via a recombinant associated adenoviral vector to the striatum of pre symptomatic H171-82Q transgenic HD mice. This led to a rescue of behavioural performance, reduced pathology both intracellularly and in terms of cell death and atrophy. This occurred 11 weeks after bilateral striatal injection of the trophic factor when the GDNF was widely distributed across the striatal complex as well as in afferent structures to it, showing robust expression several weeks after delivery. In addition the ability to prevent pathology was striking in contrast to some other studies using different transgenic mouse models of HD. However, whilst the mechanism by which GDNF achieves this effect is still unresolved, it adds to the emerging role of neurotrophic factors in HD including recent studies on the effect of huntingtin on BDNF and the value of encapsulated cells releasing CTNF as a potential treatment. -RAB

McBride JL, Ramaswamy S, Gasmi M, Bartus RT, Herzog CD, Brandon EP, Zhou L, Pitzer MR, Berry-Kravis EM, Kordower JH.

Viral delivery of glial cell line-derived neurotrophic factor improves behaviour and protects striatal neurons in a mouse model of Huntington's disease.

PROC NATL ACAD SCI USA

2006;103:9345-50.

STROKE: upright or left?

*** RECOMMENDED

There are a number of reasons why balance may be affected after stroke and, if asked, therapists may cite both sensory and motor contributing factors. However balance is often treated without consideration to perception, just by practicing staying upright or responding to perturbations. This may not be the most intelligent approach – if the underlying problems are not fixed then maybe balance will not improve. An interesting investigation by Bonan et al has revealed that subjective visual vertical (SVV) perception is often abnormal after stroke. SVV perception is measured by sitting subjects in a darkened room and asking them to adjust a luminous line to vertical. It was found to be abnormally tilted in 12 out of 30 stroke patients. In addition, 12 patients showed more uncertainty than normal (ie. greater standard deviation) in the judgement over eight trials. There were significant but unimpressive correlations with balance performance. SVV was more uncertain in patients with right hemisphere lesions and interestingly the amount of tilt was greater in patients with partial proprioceptive loss in the lower limb than in those with absent proprioception. These results suggest that assessment of sensory and perceptual factors may be useful for planning treatment for stroke patients with impaired balance and that maybe new treatments for neglect that work to recalibrate and integrate sensory inputs might contribute to restoring balance. -AJT

Bonan IV, Guettard E, Leman MC, Colle FM, Yelnik AP

Subjective visual vertical perception relates to balance in acute stroke

ARCHIVES PHYSICAL MEDICINE REHABILITATION
2006;87:642-6.

PARKINSON'S DISEASE (PD): switching off pathology

Novel strategies for treating Parkinson's disease have been something of a theme in the journal review section of the ACNR and one exciting new initiative involves the silencing of pathogenic genes/proteins in PD using small interfering RNAs. This has been tried before in diseases of clear genetic origin such as Huntington's disease and spinocerebellar ataxias, but in a new paper in *Experimental Neurology*, Martha Bohn and colleagues have applied this new approach to alpha synuclein - the protein that characterises Lewy bodies in Parkinson's disease and mutations of which, along with duplication and triplications, cause familial PD. In this study synthetic siRNAs were manufactured to human synuclein and linked to a lentiviral vector. They initially showed that the interfering RNA could successfully silence human alpha synuclein protein expression in various cell lines, including the catecholaminergic SHSY51 cell line. Finally, they virally overexpressed human alpha synuclein in the striatum of the adult rats and showed that their interfering RNA could switch production of the protein off two weeks later.

This is an important study because it highlights the possible efficacy of this approach in PD and other synucleinopathies. However many problems still exist with this approach, including switching off the gene in idiopathic Parkinson's disease where it is not mutated or over expressed, not switching off the normal form of alpha synuclein given its presumably vital role in normal synaptic homeostasis and, thirdly, managing to give long-term delivery of such factors to multiple brain regions achieving silencing to a significant extent over years. Thus whilst this study shows the value of this approach in neurodegenerative disorders it raises more questions than it answers. -*RAB Sapru MK, Yates JW, Hogan S, Jiang L, Halter J, Bohn MC.*

Silencing of human alpha synuclein in vitro and in rat brain using lentiviral-mediated RNAi

EXPERIMENTAL NEUROLOGY

2006;198:382-90.

EPILEPSY: not all spikes mean fits – take a family history

*** RECOMMENDED

We are all familiar with the patient who presents with a blackout and a strong family history of idiopathic epilepsy. On one level this increases the chance of the patient also suffering epilepsy. On another level it increases the chance of asymptomatic EEG changes, which need to be interpreted with caution. The extent of this potential problem is illustrated by the current study, which also highlights the significant number of symptomatic patients with presumed IGE whose EEG may be normal. In this study there were 31 probands with a secure electroclinical diagnosis of JME and 149 first-degree relatives, of whom 132 had a sleep-deprived EEG. Two of 52 parents (4%) were symptomatic and 13 of 68 siblings (20%), a total risk of 13% for first degree relatives. The clinical syndromes were JME (44%), epilepsy with grand mal on waking but no history of myoclonus (19%), childhood absence epilepsy in one patient and one with GTCS with no particular pattern. Of the symptomatic relatives, only 6 (37.5%) had a definitely abnormal EEG, with a further 12.5% with borderline changes and 12.5% with some focal abnormalities. Of the 106 asymptomatic relatives, seven (6%) had spike and wave on their EEG and a further 6% had borderline changes. This study supports previous studies in showing a major genetic component to this common syndrome. The high incidence of asymptomatic EEG changes in first degree relatives reminds one of the importance of a family history. It also begs the question: if these patients were followed up for long enough, would they have seizures? The study does not answer the question of the risk of epilepsy in the offspring of those with JME, which has been addressed previously. -*MRAM Jayalakshmi S, Mohandees S, Sailaja S, Borgohain R.*

Clinical and electroencephalographic study of first-degree relatives and probands with juvenile myoclonic epilepsy.

SEIZURE

2006;15:177-83.

STROKE: good old rat poison for atrial fibrillation

*** RECOMMENDED

In the "ACTIVE W" trial, co-ordinated in Canada and executed all over the world, people with atrial fibrillation and one other risk factor (previous stroke or TIA, hypertension and poor ejection fraction for instance) were randomised to receive old fashioned warfarin (target INR 2.0-3.0) or new-

fangled aspirin and clopidogrel together. The study was started in June 2003 and was stopped early in August 2005 by the data and safety monitoring board because of clear superiority of warfarin. Within the 6706 randomised patients, there were 165 primary outcome events (stroke, arterial embolus, MI or vascular death) in the warfarin group compared to 234 in the aspirin/clopidogrel arm: an annual risk of 3.9% versus 5.6% and a number-needed-to-treat of 48 (my calculation). Rates of major haemorrhage were identical in each group; interestingly, total bleeds were more frequent in the aspirin/clopidogrel cohort. The accountants will be delighted: a year of warfarin costs roughly £20 whereas clopidogrel with aspirin sets you back £1,600. The ACTIVE W study is one third of a complicated triptych of clinical trials. ACTIVE A examines the effect of adding clopidogrel to people already receiving aspirin and ACTIVE I adds irbesartan to cohorts from the W and A trials....they are still being processed. These studies are funded by the manufacturers of clopidogrel and irbesartan: the Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. -*AJC*

The Active Group.

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial.

THE LANCET

2006;367:1903-12.

EPILEPSY: life through blue tinted spectacles

Case history: The patient comes through the door with a history of blackouts and is wearing blue tinted spectacles. And the diagnosis is..... if you say non-epileptic seizures then this paper may change your mind. Photosensitivity triggers seizures and anxiety in high risk situations for susceptible individuals. The authors took 610 patients, median age 11.9 and two thirds female with proven type IV photoparoxysmal response on EEG and repeated their test whilst wearing Z1 lenses. These lenses are commercially available in Italy and attenuate light by over 90% in the range 480-600nm wavelength. The abnormal response to photic stimulation was abolished in three quarters of patients and significantly attenuated in a further 18%. The authors argue that patients who only have seizures in response to photic stimuli may prefer treatment with spectacles to medication, whereas those who also have seizures at other times will require additional medication. Not all photosensitivity is reproducible with photic stimulation but this paper suggests that a significant number of patients may be helped in this way.

-*MRAM*

Suppressive efficacy by a commercially available blue lens on PPR in 610 photosensitive epilepsy patients.

Capovilla G, Gambardella A, Rubboli G, Beccaria F, Montagnini A, Aguglia U, Canevini MP, Casellato S, Granata T, Paladin F, Romeo A, Stranci G, Tinuper P, Veggiotti P, Avanzini G, Tassinari CA.

EPILEPSIA

2006;47:529-33.

STROKE: aspirin and dipyridamole.... The business?

I must admit to a heart-sink feeling when faced with trials like this in my favourite magazine. I know I ought to be interested... and they are all terribly worthy... but somehow they fail to excite the imagination. Ah well, at least this one is an academic study; you can tell because it has a long follow-up, poor patient retention and no drug company sponsorship.... The question being considered is whether your patient benefits if you prescribe dipyridamole (200mg bd, mainly slow-release preparation) in addition to aspirin for the secondary prevention of stroke or TIA. 2739 patients were randomised, mainly in the Netherlands and the UK. During the 3.5 years of follow-up, primary outcome events (fatal and non-fatal ischaemic stroke and all cardiac events) occurred in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone. Although fantastically significant statistically, this gives a number of 104 (95% CI 55-1006) patients per year needed to treat with the combination regimen to prevent a death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication. This amounts to about £10,000 per event prevented: a local NHS hospital has already declared that this is "uneconomic". Now that really is a scandal. -*AJC*

The Esprit Study Group.

Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial.

THE LANCET

2006; 367:1665-73.